SCIENCE

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AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

Dr. John R. Low, Jr., B.S., Purdue; D.Sc., Carnegie Tech (1943), served on the faculty at Pennsylvania State Univ. before coming to General Electric in 1948 as head of metallurgy research at the Knolls Atomic Power Laboratory. In 1953 he joined the staff of the General Electric Research Laboratory, where he is a member of the *Alloy Studies Section.*

Searching for safer metals

Dr. J. R. Low, Jr., of the General Electric Research Laboratory, provides theories to explain the fracture of materials

A history of wintertime tragedies involving broken ships, collapsed bridges, and ruptured pipelines testifies to the importance of understanding why metals break as they do. Dr. J. R. Low, Jr., of the General Electric Research Laboratory, began his attack on the problem of *low-temperature fracture* by looking for the very first evidences of cracks in a stressed-metal sample. He found that tiny breaks — microcracks — actually are present in the grains of the metal well before catastrophic failure occurs.

Recently, Dr. Low has been able to assemble the known facts about fracture into a consistent theory and thus has provided a mathematical relationship between the grain size and the brittleness of metals.

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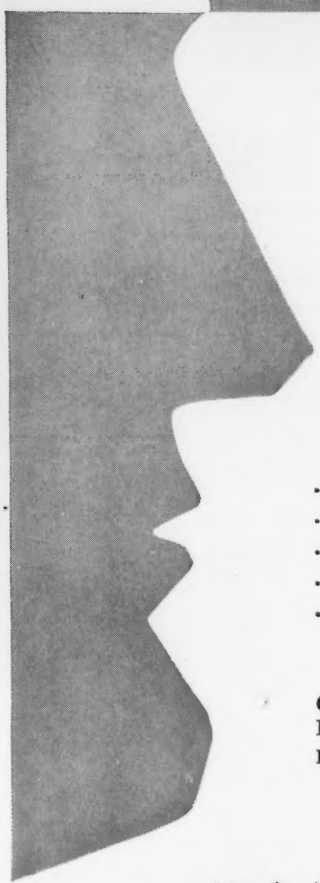

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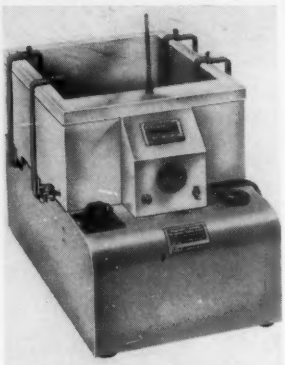

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(2) Ind. & Eng. Chem. 25-1112 (Oct., 1933)
(3) National Bureau of Standards Journal of Research 12-241 (Feb., 1934, R. P. No. 649)

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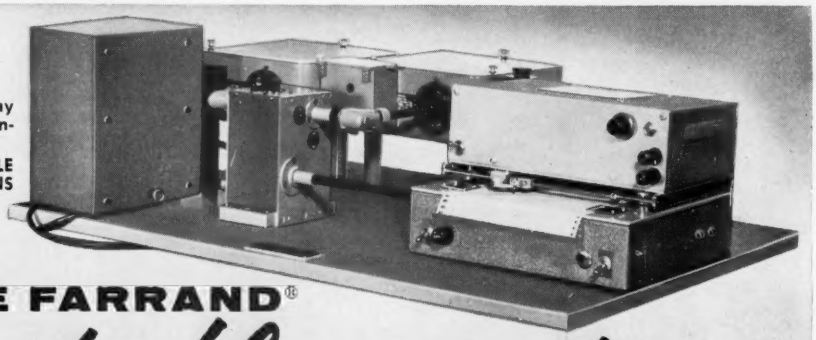

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Governmental Indemnity

The development by private industry of economically competitive atomic power plants requires a certain state of confidence as well as of technology. Despite an impressive published safety record both in this country and abroad, the possibility of a catastrophic accident remains. Measured in dollars and cents, admittedly an inadequate index at times, the fear of this possibility is sufficient to discourage private investment, for if such an accident did occur, the cost in damages to the general public might well put the company or companies involved out of business.

Other investments have their risks, with businessmen ordinarily able to share that risk with other investors on the basis of the laws of chance, each investor paying a premium now to insure that later he will not be subjected to a greater loss. The big insurance companies believe that by pooling their interests they will be able to offer substantial coverage to the operators of atomic power plants and the manufacturers of atomic equipment. Testimony last spring before the Joint Committee on Atomic Energy put the sum that the insurance companies could pay out for a given accident between $50 and $65 million, which is about 5 times more than the highest liability policy previously issued.

Impressive as is the response by the insurance companies, it still does not solve the problem unique to atomic power. Other testimony before the committee revealed that if a reactor failure occurs in which fission products escape from containment structures into the atmosphere, the resulting cost in radioactive contamination to the neighboring areas and in radiation injury to persons might be considerably higher than the protection afforded by the insurance companies. For example, Willard F. Libby estimated that the worst of all possible disasters in a 100,000-thermal-kilowatt reactor might cost in property damage alone from $50 to $200 million. Of course, the great size of this figure, and the possible radiation injury to persons, must be balanced against the probability, which Libby called "vanishingly small," that this awful event will take place.

One way to encourage the private development of an atomic energy industry is for the Federal Government to assume part of the risk. A bill prepared by the committee and introduced in the Senate last June by Clinton P. Anderson (S. 4112) and in the House by Melvin Price (H.R. 12050) provides until 1 August 1966 for a measure of governmental indemnity. In return for a reasonable charge, the United States will agree to pay up to $500 million for damages above the amount covered by private insurance, with the cost of any additional damages to be handled by special legislation.

Some people have strong convictions concerning where to draw the line between governmental interference in private enterprise and governmental action in the interest of the general welfare and national security. But if there are to be atomic power plants, an experimental spirit is necessary here as well as in such matters as reactor design. In our opinion, the bill now on the calendar has been offered, and should be enacted into law, in that spirit.—J. T.

(Left to right) Dr. John Bardeen*, Dr. William Shockley* and Dr. Walter H. Brattain, shown at Bell Telephone Laboratories in 1948 with apparatus used in the early investigations which led to the invention of the transistor.

Bell Telephone Laboratories Salutes Three New Nobel Prize Winners

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Such achievements reflect honor on all the scientists and engineers who work at Bell Telephone Laboratories. These men, doing research and development in a wide variety of fields, are contributing every day to the improvement of communications in America.

**Dr. Bardeen is now with the University of Illinois, and Dr. Shockley is with the Shockley Semiconductor Laboratory of Beckman Instruments, Inc., Calif.*

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11 January 1957, Volume 125, Number 3237 SCIENCE

Professional Collaboration

Vannevar Bush

It is my purpose in this paper to examine some of the responsibilities and opportunities of the professions, particularly those of medical men and scientists in these days of great hazard and promise.

A fascinating future surely lies before us, provided that we can escape certain perils, and the most heartening potentialities lie in the field of medicine and in the sciences adjacent to it. The time is coming when the practice of medicine will rest securely upon a firm scientific foundation, upon a systematic understanding of the life-processes in all their complexity, and no longer upon the insecure and shifting basis which partially supports it today, with clear understanding in part, but with a great mass of uncoordinated, empirical data necessarily as the main reliance.

The full integration may not come in our lifetime; indeed, in the light of the enormous complexity of living organisms, its consummation may require more than the mere compilation of experimental facts and the orderly marshaling of them under working hypotheses, the method which has been successful in the far less arduous task of interpreting the mechanical aspects of the nature of the physical world. There may be required new methods of thought, novel ways of recording and transmitting the accumulated experience of the race, ways as yet unconceived of bringing to bear on complex problems the interrelated efforts of diverse minds. We may witness new devices as powerful, versatile, and rapid as digital computers in the realm of computation and analysis, but capable of interrelating and ordering masses of primary and inexact observations into meaningful arrays. There may be means for communicating the knowledge of a group which will render obsolete the cumbersome writing of papers and the chaotic task of storing and consulting them. Certainly we will see the day—perhaps we should have already—when the public lecture is fully obsolete.

The marks of progress are all about us. The biological sciences are moving forward on a broad front and at an accelerated pace. In the next decade the flood of accumulated basic knowledge may produce applications of startling moment, much as the accumulated fundamental knowledge in physics recently led to an understanding and manipulation of the atom, the transmutation of elements, and controllable atomic energy.

Genetics some 10 years ago turned from the higher organisms to more elementary ones, expecting to find there simplicity in the beginnings of genetic systems, and found instead an amazing early complexity. But, with the more plastic material, experimentation has proceeded at a breath-taking pace. Chromatography, the use of tracer elements, and michrochemical processes are sorting out many an old puzzle in biochemistry. The involved system by which bacteria synthesize the amino acids is falling into line, and some day we shall understand more of how these building blocks are assembled into proteins. The amazing skill of organic chemists produces for us not only duplicates of vitamins or hormones, but also derivatives and analogs of these, and we understand the first chapter of how an antibiotic may operate, or why a vitamin is essential as the building block for an enzyme. The chemistry of muscle action is not nearly as mysterious as it was; at least we know something of the source of energy and something of the process by which chemical bonding and shortening are interrelated. In photosynthesis it appears that we are, at last, on the verge of producing the essential chemical action *in vitro*, with chlorophyll and its associated protein isolated intact for our study.

We could readily extend the list of recent accomplishments. But there is vastly more to be done. We are, for instance, very far from understanding why one substance, with a molecular weight in the millions, may be beneficial, while another, differing only slightly, may interrupt essential life-processes. The world is still full of mystery, and it will be long before we understand much, even when we limit ourselves to the mere mechanism of life and do not approach that greatest mystery of all: that we, as conscious beings, are capable of pondering it all.

As we view how far we have come and glimpse the great vistas before us, we know that this is an exciting time in which to live and that stirring adventure beckons. There is accomplishment to be made that will render life more pleasant and we hope more fruitful, that will lift the burdens which man's shoulders have borne since he first dominated the earth and banish the pain and harassment that have always been his lot. For we now know that, given time and wisdom, the ills of man may be conquered, even those ills of his mind which have forever dragged him down. All this can be done if we escape our perils and continue on the bright path we have recently trod.

And what are these perils? First is the threat of war, appalling war that would be fast and terrible, in which H-bombs would destroy cities at a blow, in which hundreds of millions would be killed and maimed in an insane fury that would leave the whole world, belligerent and neutral alike, a devastated desert.

This is not the only peril. The *Communist Manifesto*, which declares, "They openly declare that their ends can be

---

Dr. Bush retired at the beginning of last year from the presidency of the Carnegie Institution of Washington. He now maintains an office at Massachusetts Institute of Technology. This article is based on the 11th Martin memorial lecture, which was delivered 8 Oct. 1956 before the meeting of the clinical congress of the American College of Surgeons in San Francisco, Calif. The lecture is being printed simultaneously in the *Bulletin of the American College of Surgeons*.

attained only by the forcible overthrow of all existing social conditions," is still the charter of a powerful oligarchy that holds great nations in thrall. Political murder, enslavement, and conspiracy against neighbors did not end when Stalin was vilified. The advancing tide of Soviet domination, engulfing weak states by force or stealth, seems to have been momentarily halted, but it will again creep forward unless we are alert.

Nor is our democratic system safe without the eternal vigilance that is difficult to sustain in prosperous times. When all goes well, as it does today, citizens are prone to forget that a determined, informed public opinion is our only guarantee that the liberties won by our fathers will not be whittled away. We have the highest standard of living the world has ever seen. We have nearly full employment, many benefits that ameliorate the lot of the unfortunate, safeguards against the cruelties of nature, and some safeguards against the evil deeds of men. But can we hold on this high plateau, continue to provide liberally for those in distress, and, particularly, can we continue our insatiable national appetite for luxury, without forcing ourselves again into inflation?

Characteristics of a Profession

Whether we escape the perils and continue on the bright path to a happier life depends on whether we, as a people, think wisely and well. Not the acts of legislatures, not the pronouncements of courts, determine our future; these are transitory and can change. The great swelling voice of the mass opinion of the citizens of this republic, incoherent and discordant, erratic and superficial as it sometimes is, and rising to heights of sound judgment at rare intervals, maps out the road that all public servants ultimately follow.

This public opinion is not formed by the radio and the press or even by those who control these media. It is formed by that minute fraction of the population which thinks and speaks, by that small but powerful minority, disagreeing on every issue, arguing and ridiculing, which looks beyond the diversion of the moment and influences because it labors to understand. The members of the minority are in every station of life—in business, in labor organizations, and on the farm. They speak in every circle. The most significant group of those who think well is in the professions, for it is their prerogative, their duty, to think for their fellows within the limits of their diverse specialties, and they instinctively approach every question by attempting to understand it, for this is the way in which they gained admission to their privileged status. On the professions, then, rests much of the burden of guiding this country of ours on its strange but hopeful way.

What is a profession? What are the characteristics by which it is distinguished from other groupings or types of organization?

First and foremost, its members are the possessors and custodians of a special field of knowledge, acquired by long, assiduous study, and they are respected and accorded privileges because of that fact.

Second, it is a loose grouping of individuals rather than a pyramidal organization. In nature we find two types of organization, the integrated society, exemplified by the ant, and the associative society, illustrated by the flock of birds in migration. Both forms have been successful in evolution throughout the wide range over which organisms combine. Both forms are found among human institutions. The profession, most decidedly, belongs in the second category. This is not negatived by the fact that many professional men are members of other types of organization and, for example, derive their income in the form of salary rather than of fees, although the true status of some professions is threatened a bit by the trend in this direction. Whether a man can be an employee, and at the same time a truly professional man, depends on whether he can maintain his individuality and his relative independence, and many can. The true profession, however, is a voluntary binding together of independent members, deriving none of their sustenance from the association, utterly uncontrolled in their thoughts and actions as long as they remain within the law and within the code of the association itself.

Third, every profession has, to some degree, a symbolism and a ritual of its own. There is not so much of this in recent times, for many procedures which were once impressive are so no longer, because we have become more mature perhaps, or at least more skeptical.

Fourth, there is often, especially in the older professions, a means for maintaining standards and for disciplining those who violate a code, usually backed up by the civil law. Something of the sort is essential, for every profession is surrounded by charlatans, and, human nature being what it is, special privileges are bound to be abused. Of course these controls have been used at times to limit the professional privilege to the elect and hold down the numbers of those who enjoy the franchise, but this is certainly not a prominent feature today. On the other hand, the formalism and rigidity of control does seriously hinder the man who would enter the profession by an unconventional path, no matter how intelligent and devoted he may be, and it tends also toward an undesirable uniformity and standardization.

But the primary characteristic of a profession has not yet been mentioned. Without it, no group, no matter how scholarly it may be, no association, no matter what the titles of its members, no assembly of striking individuals, no matter what may be the depth of their culture, is truly entitled to the proud name of profession. From the earliest times, this primary characteristic has been the hallmark of professional men when such men have lived up to their high ideals. The members of a profession minister to the people. The word connotes more than service. *To minister* implies no servility, no apology, no inferiority. On the contrary, members of a profession minister with dignity; they demand the respect due to their skill and devotion; they do not merely advise, they insist upon being heard; they do not submit their opinions for the judgment of the layman who is their client, no matter how powerful he may be; they insist that they have his confidence and that, in their special field, their opinion shall control, or that the client turn elsewhere. They recognize that he may need to join their findings with factors outside their special field in coming to decisions. They refrain, if they are wise, from any appearance of speaking with authority except in the area of their own competence. But within their proper scope, modest men though they may be, they advise and guide with pride, and with the insistence that the ancient art which they represent be received with the respect which is its due. And, when they minister to the weak and humble, they do so with kindness, bringing to the unfortunate, whether their ills are spiritual or physical, whether their misfortune results from the rigors of nature or the cruelty of man, that most heartening of support, a strong and able ally and friend on whom to lean. All this it means to minister. As long as members of our professions live up to their birthright, this will be the shibboleth that strengthens the bond among them.

There is a corollary characteristic. The true members of a profession detach themselves from the mad scramble after this world's goods. This does not mean, as it once so often did, that they abjure the fine things of life and retire into a monastery. In order to function with full effectiveness, a professional man needs a competence, that he may live in reasonable and proper manner, as befits his station and his mission. But when a man in the professions makes riches his primary goal, he ceases to belong to the profession in a true sense. The greatest exemplification of this corollary charac-

teristic lies among the humble members of religious groups—the devoted parish priest, the preacher whose flock, with their sorely troubled minds, is his primary concern, and to whom wealth, or even a proper income, has no meaning in the light of his devotion.

But this article is concerned principally with other professions, for religion stands by itself and should not be subjected to the analysis which applies elsewhere. And there are plenty of examples in other fields. The teacher, and there are many, who cannot be lured by any salary attraction to less satisfying fields from the joy he finds in aiding the development of young minds is all about us, and in fact we would be in a sorry plight without him. The lawyer who takes special satisfaction in protecting the indigent and the misunderstood, sometimes at the peril of his reputation, is known to all of us. The able and devoted country physician on his weary rounds needs no emphasis on his character.

Privileges

We speak of the privileges of the professions, and it is well to examine their basis and practice briefly. There are first the legal privileges, set up to protect the public against charlatans and salesmen of false service, and very necessary for the purpose: admission to the bar, the registration of engineers who deal directly with the public, and the license to practice. Systems, tests, and certification are essential whenever the choice of advisers is directly exercised by individuals, and we certainly, in this country, do not wish to replace this free choice by some form of bureaucratic assignment. In general, our procedures for public protection work well, even though they are occasionally viewed as a means for protecting the members of the profession themselves rather than the people they serve.

Let me, in all frankness, speak of this for a moment. Every profession, in order to function in a modern environment, is surrounded and supported by auxiliary groups, the technicians and semiprofessional groups who are the hewers of wood and drawers of water, but whose performance is nevertheless fully important to sound over-all results. These groups are not always treated with generosity and wisdom by the professions they serve. I might choose my examples from various fields—from the teaching profession where arbitrary linking of promotion and academic degrees is often carried to absurd extremes, from research laboratories where the skilled instrument maker who makes a result possible is given a curt nod rather than the recognition he has earned. Artificial barriers are foreign to our democratic philosophy, and they are gradually disappearing. Even in the military profession, an enlisted man occasionally becomes a general, and such examples, while rare, accomplish much in the improvement of morale throughout the organization.

It seems to me, as I view it from a distance, that the medical profession has much yet to learn before it is fully in step with the trend in this regard. Is the skilled technician who makes himself master of an intricate procedure, who is scholarly and wise, and who can, perhaps, manipulate tagged iodine for the thyroid better than the one who originally conceived the method, nevertheless, doomed to remain permanently in an inferior status, merely because his path to understanding was unconventional? Is the nurse of superior judgment and devotion accorded the full professional recognition that her caliber warrants? I know an accomplished archeologist, an eminent astronomer, and a number of outstanding engineers who never took a degree in course, but I do not know an eminent medical man who rose through a fully unconventional route. Ah, one says, but the system for protecting the public has to be far more effective in the medical field than elsewhere. I agree. But it does not have to be rigid and arbitrary in order to be effective; in fact, the two seldom go together.

I suppose we always need somewhat more positive limitations on designation of those who are entitled to prescribe or operate directly for fees. But I do wish that there were carefully guarded side entrances to the chosen circle as well as the well-marked front door. And, more to the point, I wish that the profession had more adroit ways of admitting to full acceptance, as special colleagues, those who excel in serving it well. I wish, also, that I could detect a trend toward passing on to auxiliary groups as much as possible of responsibility and of elevating activity, for the medical system is not one group but a number of interrelated ones, and its health is dependent on the morale throughout them.

The greatest privilege which a profession enjoys is not the prerogative conferred by law but the respect accorded its members by a grateful public, and, when a profession becomes intricately organized in the modern sense, it is essential that this unique privilege be shared throughout the groups involved in order to foster the pride and loyalty which alone can maintain the discipline and smooth interrelation needed for satisfactory performance. It is also essential, it seems to me, that there be no rigid caste system based on birth or youthful path of education, in which individual status is absolutely controlled until death, but a more fluid situation in which there are no barriers that cannot be surmounted by intelligence and hard work.

Responsibilities

What of the responsibilities of the professions, which accompany the privilege? We have already considered the primary responsibility, to serve well, to minister to the public with dignity and skill, in the fields which are their several domains. To this we have added another responsibility, secondary to the first, but of equal significance, the responsibility to lead their fellows in their consideration of public questions and in the intricacies of their daily lives. Upon the wisdom of those who thus lead, wherever they may be placed, whatever the competence which causes their associates to turn to them when puzzled, depends the safety of this country in a hazardous and promising world. There is a duty inherent upon those who can talk well to do so, and to make their thoughts known, to differ widely upon every question, with faith that an informed public opinion can resolve differences reasonably.

For the professional man, this often presents a quandary; it is sometimes difficult for him to speak without his hearers' being given the impression that he regards his eminence in one field as conferring upon him a special status in all fields. In fact we see, occasionally, the man of the physical sciences who speaks ex cathedra on politics or economics, and who thus debases the currency of those who would express honest opinions as laymen in problems where every citizen is entitled to participate and none is entitled to arbitrary judgment. But our complex modern affairs need more analysis by thoughtful men, and wide disagreement of opinion on public questions, outside of the professional field, is not inconsistent with the presentation of reassuring unanimity on well-accepted doctrine within it.

There is another responsibility of any profession, and this brings us back to my original theme. This is to enhance and extend the knowledge and understanding on which the professional practice of the profession is based. In the case of medicine, this means the profound task of understanding life, its origins, its chemical and physical processes, and its manifestations in man in his whole range of mental and physical ills and health.

The subject is too vast for any one individual or any one group; the skills and instrumentation from diverse fields are essential for progress. And all this calls for more and more effective collaboration between the medical profession and

the scientific profession, especially that part of the scientific profession whose subject matter is adjacent to medicine. I feel that such collaboration is today lacking or faulty in too many instances, and I am anxious to determine, if I can, the reasons for this situation.

There are areas where good collaboration occurs, of course. In industry, in the pharmaceutical field in particular, I have the impression that medical men and scientists understand one another pretty well and work together reasonably effectively for common ends. Then too one can point to isolated cases where there is effective attack on problems by joint effort, because two individuals happen to speak the same language and supplement one another's skills smoothly. But there is not enough of it. I cannot think of many cases in which a physicist, for example, of top caliber and a medical man of equal status have jointly attained an important result that would have been inaccessible to either alone, and where the collaboration has been on a basis of full equality and understanding. And I believe this is because there are certain artificial barriers present which could readily be broken down.

Development of Collaboration during World War II

Let me examine a somewhat parallel situation. At the beginning of World War II there was almost complete lack of collaboration between scientists and military men. True, there were governmental laboratories where both types were present, but usually there was a gulf between them. True also, there were scientists and engineers in industry who worked closely with military men, but the relationship here was often that of purchasing agent and salesman rather than professional. There was generally a complete lack of understanding and an aura of myth and prejudice.

Military men thought of scientists as long-haired visionaries, with no comprehension of the tough practicalities of life in general and certainly not of war. They felt, and here they were right, that few scientists had the slightest conception of what is involved in military leadership, of the rugged indoctrination that enables a good officer to hold terrified men together, striving toward a common goal, in the face of disaster, horror, wounds, and sudden death. They felt, and here they were wrong, that scientists were generally prima donnas and softies who could not take it. Moreover, they felt sure that the art of war had matured, that technical change could come only gradually and in detail, and hence that scientists had nothing real to contribute, and moreover that they spoke a language which no normal human being could possibly comprehend or would wish to.

Of course, there were exceptions. There were Army and Navy officers who were excellent engineers and who had, as every really competent engineer must have, an understanding of the trends in the sciences on which engineering progress is based. But the main body of opinion was the other way. Early in the war a major general, whom I will be careful not to identify, but who headed a very important branch of the service, told me in no uncertain terms that research on weapons during a war was absurd, for no weapon developed during a war ever came into use before its termination. And an admiral asserted forcibly, and in writing for that matter, that the Navy had the submarine situation entirely under control and wished no suggestion from those who could not possibly comprehend its problems. Officers were generally polite, but courtesy usually connoted a feeling on their part that there was nothing to be gained by any less formal relationship.

And scientists, only too generally, thought of military men as dodos, who insisted on fighting every war with the weapons of the previous one, who resisted and resented innovations that would cause them to alter the ingrained habits and conceptions of a lifetime. Unfortunately, there was often something of truth in the concept. They regarded military men as caste conscious, with a tightly knit set of social conventions. They also felt that one could not collaborate with a military man, that all one could do would be to lay naked before him the fruit of his labors, for him to judge, without explanation and without appeal, from his unique position as the only professional man who understood war.

The relationship between medical men in uniform and out was, of course, markedly different. For many medical officers were professional medical men first and foremost, and many medical men in civilian life understood fully the problems of medicine in the services. But I have been considering the relationship on new weapons rather than on military medicine, and on this there was a yawning chasm and an almost complete lack of collaboration of any sort.

Yet, before the end of the conflict, the whole art of war had been completely transformed, because of the advent of spectacular new weapons: guided missiles, proximity fuses, radar, target-seeking torpedoes, recoilless guns, rockets, appallingly effective gases which fortunately did not come into use, and the A-bomb. Moreover, there had developed a genuine partnership between military men, on the one hand, and scientists and engineers, on the other. Mutual understanding and respect appeared. Close friendships developed. Many officers acquired a remarkable understanding of new technical developments. Many civilians became adept in the subtle aspects of the art of war. There was teamwork of the highest order, and out of it evolved a new concept of national conflict. The course of joint development has proceeded since the war, somewhat haltingly at times, but with continuing momentum, until it has now resulted in a situation which is entirely new in the world, and in which all great war is absurd and obsolete, an unmitigated disease which must be avoided by all means, for it would be fatal to civilization, rather than the last resort of diplomacy, to be indulged in when the risks appear justified.

Why was there this extraordinary transformation in the relations between two professional groups? Primarily because there was a war on, and men suppressed their prejudices and their preferences in the general national fervor and in the determination to serve well in a time of common peril. But the two groups, thus forcibly brought together, discovered that many of their prejudices and judgments were based on myth. And each group found, in the other, unsuspected qualities of character which they could wholeheartedly admire. The transformation occurred here, and in a parallel manner in Britain, because these were democracies, where gulfs of caste or pride were readily bridged. It did not occur in the Germany of Hitler or the Japan of military domination, for the highest type of partnership is impossible in the atmosphere of totalitarianism. And this is one very cogent reason why Germany and Japan lost the war.

Barrier to Collaboration

Now I am not going to present a detailed analogy between this relationship I have reviewed and the present relationship between medical men and scientists. Some of the aspects have their parallels, which you can readily recognize, and some most decidedly do not. But I do wish to point out one or two factors in the present situation to which we may direct attention, I believe to advantage, even although in so doing I may move close to the edge of that unforgivable social sin of criticizing one's host, for I do not believe we are going to make much progress in bringing the professions closer together unless we examine frankly some of the structural features of the barrier that separates them.

I dismiss at once the allegation that surgeons are too high-hatted to work

with, that traces of compensation remain from the days when they were joined with the barbers and shunned by gentlemen. Some of the same allegations are made regarding engineers, of whom I am one, for the engineer deals with costs, and the minds of true scientists are above such mundane matters. I dismiss these allegations as false at the outset so that they will not cloud our analysis. I know I am right regarding surgeons, for I have worked with many of them, and although I have found the same distribution of idiosyncracies that occurs in the general population, I have yet to find one wearing a tall hat.

Medical men, generally, feel that scientists do not understand the motivations, tensions, and inner emotions of a medical career, and they are generally right. Scientists have never walked the wards. There is a vast difference between deciding upon the contents of a syringe, upon which may hang the life of an accomplished and valuable patient, and deciding upon the contents of a test tube, upon which no more depends than the fate of a pet theory. There is a harrowing difference between looking at the position of a needle on a dial and looking into the eyes of a dying child. There is an essential distinction between the care of a patient and the treatment of a disease. Certainly few scientists have grasped the full import of these differences. But they can learn.

Medical men, generally, feel that scientists do not understand that the practice of medicine is, and must long remain, essentially an art, to which science can sometimes contribute, but which it can by no means at present supplant. They feel that scientists insist on proceeding logically point by point, pinning down one concept completely before proceeding to the next, working slowly toward a distant goal with little thought of applications on the way, whereas medicine must continuously do the best it can with what it has at hand, even though its processes are often admittedly unscientific and even crude. They feel that scientists do not appreciate this need for art, that they are contemptuous of all that does not conform to their own standards of rigor, and that they would therefore place obstacles in the road toward empirical but necessary advance.

To turn to the other side for a moment, scientists generally feel that, when a medical man and a layman are joined in an endeavor there will be no partnership in reality, but that the medical man will either dominate the combination or break it up. They feel that if the scientist tries to collaborate he will soon be reduced to the status of technician, and that, if results appear, they will inevitably become attributed to the member of the group who alone is privileged to deal directly with the essential ultimate subject matter, human life. They feel that the medical man is afraid to admit ignorance, even when justified, and that he tends to protect himself by overassertion.

Now let me assert at once that in regard to this preconception, and the others that I have just treated for that matter, there are many exceptions, many in each profession who understand and appreciate the opposite profession fully. But I am dealing in generalities, and, in this sense, there is unfortunately a real basis for the feeling which I find among scientists rather generally. And it is not, after all, too surprising to find this true. The medical man, if he is worth his salt, and by reason of his training and experience, is prone to assert himself. If he enters a home where there is a sudden critical illness, he must portray calm and confidence, however he may feel inwardly. If he enters upon a hazardous operation, he must insist that every move in the operating room be centered about and responsive to his personal needs and decisions.

And this is the aspect of medical characteristics which the layman usually sees. He does not see the small conference between medical men on a tough case, where there is full discussion and give and take, where the opinion of the most junior member is treated with respect if he can support it ably, where there is no organization, and no one is boss, even although one man alone may be called upon to resolve the discussion and render the final decision. Still, and to be fully frank, I believe there is a bit of real basis for the feeling that, where a medical man is joined with other professions, he instinctively tends to take over.

The essence of collaboration is the suppression of all instinct toward the establishment of a pecking order—in fact the enjoyment of any social grouping whatever depends intimately on the complete absence thereof. In relations between professional men there is no such crude and elemental concept involved. But, since its presence or absence is so determining in our judgment of human relations, even the remote suggestion that a sublimed form may be present destroys the effectiveness of collaboration, for collaboration means the substitution of a group objective, voluntarily accepted, for the individual objectives of the members.

Breaking the Barrier

I could go on and try to examine a few more structural members in the barrier. But what do we do about it?

In the first place, let us record that there are individual members of every profession who will never collaborate with anyone under any circumstances. Let them depart in peace; their day is nearly done. The time is over when a Leonardo da Vinci could comprehend all of known art and science. We are also past the day when men of genius could retire to a cubicle, exclude all, and emerge with an intellectual feat of scientific reasoning before which all would bow in humble admiration. Even in the remotest corners of extreme specialization, where isolated contributions springing full grown from a master mind are still possible, the most notable advances are made under conditions where mind works on mind and where credit for primary initiation is sometimes hard to assign. The man of genius still is the most important element in the whole array, and upon his excellence most of progress depends, but if he does not know how to collaborate or is too selfish or timid to do so, we can safely forget him.

We cannot order collaboration. This is not a dictatorship. Moreover, while shotgun marriages sometimes turn out surprisingly well, shotgun collaboration is a contradiction in terms. And no amount of artificial organization, no joint institutes, or combined reviewing committees, or joint directors, will come within the squirting range of a syringe of getting at the heart of the matter.

I have only one prescription, and I cannot write even this one in Latin. The professions fail to understand one another sufficiently; let us attempt to bring them together. We do not have the impulse of war to force men into contact, and hence it will take long to produce a detectable improvement in relations by this means. Yet I see no other path.

Now I do not mean more joint professional meetings; not that! If they occur I would expect them to widen the gulf more completely. Nor do I have in mind lectures by a member of one profession for the edification of another. I am skeptical of the value of all lectures. I would hope that we might approach, much more nearly than any such artifices as those, the core of the dilemma. And that resides in the misconceptions which each profession has in regard to the other.

If I were speaking to a group of physicists, I would have a suggestion to make. I believe it would help a bit if medical men, those who do not already understand it, were given an exemplification of scientific research in action and at its best. I am far from advocating in this connection more popularization of science, or more interpretation of science in one field for those in neighboring fields, although such steps have merit. I wonder if one could reconstruct the meeting in 1939 at which the news of a cru-

cial experiment and the ideas of Frisch and Meitner were communicated to a group of physicists, and from which meeting emerged the concept of atomic fission, to be confirmed by experiment in three laboratories within 48 hours.

I fear it would be difficult to recapture the genuine atmosphere, the give and take between earnest men, the tentative hypothesis which collapsed on a sentence, the subtle grasping of relationships which were hardly expressed, the symbolism which crammed into a yard of blackboard the concentrated essence of a generation of mathematics, the mounting tension as revolutionary concepts became clearly formulated and accepted. Something of the sort might be done, and I believe there is many a medical man who, if he participated thoroughly in such an affair, even on a much less ambitious plane, would learn something worth while about how the scientific mind really operates, and what is the method of scientific collaboration at its best.

I suggest, also, that it would help to join a scientist occasionally in serious, responsible discussion of a case, typical or otherwise, of kidney malfunction, or metabolic disorder, or whatever, along with the physician in charge and the staff members. At times the fresh approach, unhampered by tradition and in spite of ignorance, will come up with a clarifying comment under such circumstances. And, in the process, the scientist will grasp more fully the central importance of art in what you do, and the contributive nature of science. He will appreciate the fundamental difference between the analysis of a disease and the forced explicit treatment of a specific case.

Thus there can be a closer approach by each group to the mental processes of the other. But I would go further than this, even though some feel that I may be naive in my approach to a very subtle problem. Men do not learn to understand one another merely by sharing intellectual experiences. They must meet on an emotional level if the foundation is to be built for collaboration on a high plane.

Scientists do not understand the true life of a medical man. With notable exceptions, this is certainly true. Yet all good scientists learn with facility, or else are simply scientists emeriti. Give them a taste of the medical life in its starkest rigor. I remember keenly one of my boyhood experiences, when I accompanied a country doctor through a poverty-stricken hospital. I remember also a conversation with a great friend and an eminent banker, whose maid had been injured by an automobile, and who had just seen the midnight scene in an emergency room for the first time, and whose admiration for the young internes was a joy to witness. I remember also being conducted through a ward, suitably attired so as not to embarrass the patients, with a young surgeon, and watching the devotion in the eyes of a humble woman for whom he had built a new face.

Pick a few outstanding and human scientists and give them such experience, and they will grasp a part of the world of man's experience which they have never known. I do not mean witnessing an operation, where the interest is mainly technical. I mean an introduction to that inner sanctum, where the true heart of medicine throbs strongly, that sanctum which is securely guarded against the cynicism of selfish men, and against the ribald comments of those to whom nothing is sacred. Indoctrinate well and test, communicate the password, and guide. From true scientists the response, while silent, will be all that you hope.

Now, what about this queer notion on the part of scientists, that medical men tend to try to dominate any small group brought together for collaboration. Here I do not know enough about the medical profession to prescribe, although I know quite a lot about some medical men. The ones I have become well acquainted with are entirely free of the fault. Perhaps there is no basis for the rumor. So I will have to leave the treatment of this ill, if indeed the symptoms are real and have not been misinterpreted, to medical men. It may call for properly proportioned psychiatric treatment; I am sure it is no case for surgery. It may be that it merely needs to be given a name and relegated to the category of rare diseases for which there is no cure but which are not of great social moment. Medical men will know. I merely mention that I have heard the allegation.

There are other ways, worth-while no doubt, in which the professions may be brought to a better understanding of one another. It is not necessary that they be brought to a full understanding of one another's subject matter; that would be impossible. For, if they grasp one another's mores and traditions, methods of thought, deep convictions, and motivations, there will be no further need to stimulate collaboration of the highest sort. It will occur automatically. And from it will result a surge forward on that complex task of understanding life, where the skill of all professional groups will be strained to the utmost, a new accomplishment which will place a firmer foundation under the keystone of that honorable profession to which medical men belong, ministry to the people. May that ministry always be conducted with pride and dignity. And may the gratitude of humble men always remain the primary compensation and reward.

Chemical Aspects of Enzyme Inhibition

Irwin W. Sizer

The subject of enzyme inhibition has come to the forefront in recent years because it offers the chemist the opportunity to study the nature of the active site and the mechanism of enzyme action. To the physiologist, it affords a technique for studying the functioning and coupling of enzyme systems within living cells and tissues. In its application to insecticides, herbicides, antimicrobial agents, and drugs, the concept of enzyme inhibition has not only proved fruitful but has provided a rationale for future developments in these areas. Although this article deals primarily with the chemical aspects of inhibition, major applications to medicine are discussed in which the biological effects of chemical compounds can be interpreted in terms of inhibition of particular enzyme systems.

Ever since the discovery of enzymes, it has been known that they are highly labile molecules which can be readily poisoned by a variety of agents. Modern developments date from 1928, when Quastel and Wooldridge (*1*) demonstrated the inhibition of succinic dehydrogenase by malonate and its reversal by excess succinate. The phenomenon of competitive inhibition was almost for-

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gotten until Woods (*2*) showed that the bacteriostatic action of sulfanilamide could be reversed by its structural analog, *p*-aminobenzoic acid. He proposed the concept that this vitamin was a necessary component of an essential enzyme system which could be displaced by the sulfa drugs. Since that time, the field of antivitamins, antimetabolites, and antienzymes has developed rapidly, and the mechanism of enzyme inhibition has become much better understood.

The foundation of our knowledge of the mechanism of enzyme inhibition was laid by Michaelis and Menten in 1913 (*3*). They proposed that in an enzyme-catalyzed reaction the enzyme first combines chemically with its substrate to form an enzyme-substrate compound (ES), which in turn decomposes to release enzyme end products. In much the same manner, an inhibitor can combine with an enzyme to form an inactive enzyme-inhibitor compound (EI). In the case of catalase (Fig. 1) and certain other enzymes, the reversible formation of ES and EI can be demonstrated by changes in absorption in appropriate regions of the spectrum. Although enzyme inhibition may be reversible upon removal of the inhibitor, numerous examples of partial or no reactivation can be cited.

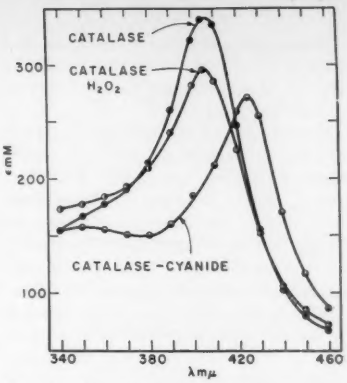


Fig. 1. Absorption in the violet region of the spectrum of catalase, catalase-peroxide compound (ES), and catalase-cyanide (EI) compound (*34*).

Mechanism of Inhibition in vitro

Although many enzymes are simple proteins, most require the presence of a coenzyme or metal, or both, for activity. An inhibitor might interfere with the catalyzed reaction in several ways (see Fig. 2): (i) by complexing with the substrate and thereby eliminating it; (ii) by combining with the protein-active groups (those that combine with substrate); (iii) by uniting with the catalytically inert part of the protein; (iv) by combining with a cofactor such as coenzyme or metal; (v) by reacting with the enzyme-substrate compound; and (vi) by a combination of the afore-mentioned ways.

In an interpretation of how an inhibitor may act on an enzyme system, an examination of the kinetics of the catalyzed reaction in the presence of inhibitor is invaluable. Variables such as *p*H, temperature, and inhibitor concentration may provide important clues, but most important is a study of the effects of substrate concentration on the inhibited system (Fig. 3).

Competitive inhibition. Enzymes are not completely specific, and they activate a family of related compounds. If the relationship is fairly close but not intimate enough for the compound to undergo reaction, then such a substance may act as a competitive inhibitor by combining reversibly with the active site of the enzyme. In a similar way, an inhibitor that bears a structural resemblance to the coenzyme may displace it from the protein surface and thereby interfere with catalysis. Since an inhibitor of this type competes directly with the substrate for the active groups of the enzyme, the ratio of substrate to inhibitor is the critical factor determining the extent of inhibition. When this ratio is high (see Fig. 3), the rate of the inhibited reaction approaches that of the uninhibited one.

In a system involving competitive inhibition, the relationship between the enzymic fractional activity α, the inhibitor concentration I, and the substrate concentration S is

$$I \cdot \frac{\alpha}{1-\alpha} = K_I + \frac{K_I}{K_S} \cdot S$$

where K_S is the dissociation constant of the enzyme-substrate compound (ES) and K_I is the dissociation constant of the enzyme-inhibitor compound (EI). A plot of this relationship (Fig. 4) enables one to measure directly the dissociation constants of ES and EI and also makes it possible to distinguish between competitive and other types of inhibition.

Noncompetitive inhibition. A noncompetitive inhibitor combines with the enzyme at a site other than the active one. Hence, the affinity of the enzyme for substrate is not altered, and no amount of substrate will reverse this type of inhibition (see Figs. 3 and 4). Since noncompetitive inhibition is independent of substrate concentration, the dissociation constant K_I of the enzyme-inhibitor complex is given by the equation

$$I \cdot \frac{\alpha}{1-\alpha} = K_I$$

From a plot of experimental data such as that presented in Fig. 4, it is possible not only to distinguish between competitive and noncompetitive inhibition, but also to calculate in both cases the dissociation constants of enzyme-inhibitor compounds. Because it is not possible to predict the type of inhibition characteristic of a particular enzyme-inhibitor system, a careful investigation will usually require the measurement of inhibition at several inhibitor and substrate concentrations. In view of the fact that a noncompetitive inhibitor may induce extensive changes in the enzyme molecule, this type of inhibition is often irreversible.

Uncompetitive and other types of inhibition. In uncompetitive inhibition, the inhibitor combines not with the enzyme but with the enzyme-substrate compound to form an IES complex. As is the case of competitive inhibition, the apparent dissociation constant of ES is decreased, but, unlike the situation characteristic of competitive inhibition, the maximum velocity at high substrate concentration is also decreased (see Fig. 5). Although uncompetitive inhibition is not commonly encountered, it, nevertheless, is important for certain enzyme-inhibitor systems.

A given inhibitor may be simultaneously effective by different mechanisms. For example, it might combine with a free active site, or a site that is already occupied by substrate, or with a group removed from or adjacent to the active site of the enzyme molecule (*4*). In addition, inhibitors may act in nonspecific ways by bringing about irreversible inactivation by protein denaturation, hydrolysis, or oxidation. Changes in *p*H may inhibit enzyme reactions by their effects on the substrate or by altering the ionization of the active groups of the enzyme. Furthermore, *p*H changes may modify the effects of an inhibitor on an enzyme (*4*).

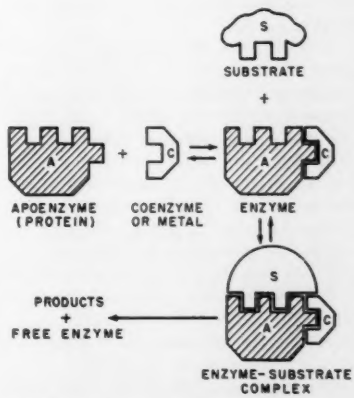


Fig. 2. Schematic diagram illustrating the pathway of many enzyme-catalyzed reactions. For some enzymes, the step involving the combination with coenzymes or activating metal is not required (modified from McElroy, *35*).

Inhibition Analysis of the Enzymatically Active Site

The architecture, composition, and properties of the groups on the enzyme molecule primarily responsive for catalysis have been elucidated by the use of inhibitors. Unfortunately, many of the group reagents are not completely specific; hence, the most reliable conclusions on the role of a particular group in the enzyme are based on inhibition studies with more than one reagent. The use of such compounds has made it possible to distinguish between the active site and that part of the protein which plays a passive role in catalysis as a carrier of the prosthetic group.

Primary amino groups. The significance of amino groups in determining enzyme activity has been investigated by inhibition studies employing reagents for amino groups of proteins. Unfortunately, most reagents are not completely specific and react with other groups such as sulfhydryl and phenol. Most commonly employed reagents for amino groups include ketene, acetic anhydride, phenyl isocyanate, nitrous acid, dinitrofluorobenzene, and formaldehyde. The roles of the amino groups of lysine vary strikingly; these groups are not essential for enzyme activity of pepsin, β-amylase, trypsin, and chymotrypsin, but they are required for α-amylase and alkaline phosphatase (*5–7*).

Carboxyl groups. Information on the role of carboxyl groups of aspartic and glutamic acids in the active site is fragmentary because of the difficulty of chemical reactions with carboxyl groups under mild conditions. Esterification with methyl alcohol or 1,2-epoxides suggests the importance of carboxyl groups in ovomucoid and crotoxin. On the other hand, the C terminal groups are not essential for the enzymatic activity of chymotrypsin (*7, 8*).

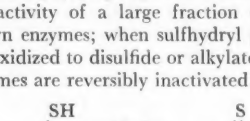
Phenolic groups. Acylating agents and nitrous acid react more rapidly with amino than with phenolic groups. Iodine reacts primarily with phenolic groups but also with imidazole and indole. In certain enzymes in which tyrosyl groups are exposed, they may be oxidized by tyrosinase, which is specific for phenolic groups (*9*). By the use of different reagents, the conclusion has been reached that free phenolic groups are required for activity of β-amylase, pepsin, chymotrypsin, phosphatase, thrombin, and invertase, but not required for trypsin and certain other enzymes (*6, 7, 9*).

Indole groups. The lack of inhibitors specific for indole groups of proteins renders difficult the assessment of the role of tryptophan in enzymes. Under certain conditions, iodine and formaldehyde react with indole groups of proteins. Peroxidase is capable of inactivating such enzymes as chymotrypsin, invertase, and β-amylase (*9, 10*), and this inhibition appears to be the result of the oxidation of indole groups.

Imidazole. The extensive investigations of the mechanism of action of nerve gases including tetra-alkyl pyrophosphates, dialkyl *p*-nitrophenyl phosphates, and dialkyl fluorophosphates have revealed that these compounds are powerful irreversible inhibitors of esterases, including proteases. It appears that these inhibitors phosphorylate a basic group in the esteratic site of the enzyme (*11, 12*). At first it was suggested that serine residues were involved in the reaction with nerve gases, but more recent work implicates imidazole groups. The inhibition of certain enzymes by mustard gas, nitrogen mustards, and diazonium compounds may be due to their reaction with imidazole as well as with other groups.

Sulfhydryl-disulfide. Of all the groups on the enzyme molecule, the sulfur of cystine or cysteine has been most extensively studied and appears to be of utmost importance in enzyme-catalyzed reactions. Perhaps one reason for the excellent information available is the wide choice of inhibitors. Metal ions (for example, silver and copper) accelerate the oxidation of sulfhydryl groups, as do oxidizing agents such as ferricyanide, porphyrindin, iodine, mustard gas, *o*-iodosobenzoate, unsaturated ketones, and quinones. Alkylating agents such as iodoacetamide and methyl bromide, and mercaptide-forming compounds including organic arsenicals and *p*-chloromercuribenzoate are useful agents for sulfhydryl groups (*13*).

Results with these reagents indicate that sulfhydyryl groups are essential for the activity of a large fraction of the known enzymes; when sulfhydryl groups are oxidized to disulfide or alkylated, the enzymes are reversibly inactivated:



Active enzyme Inactive enzyme

Reducing agents such as cysteine, thioglycollic acid, ascorbic acid, hydrogen sulfide, glutathione, and 1,2-dimercaptopropanol (British antilewisite, BAL) are effective in restoring activity. The case of glyceraldehyde-3-phosphate dehydrogenase deserves special mention because the essential SH group belongs to glutathione, which is firmly bound to the protein (*14*). The sensitivity of SH enzymes to oxidation-reduction potential suggests a physiological means of controlling the activity of these enzymes inside living organisms.

It might be surmised that certain proteins would require the disulfide bond for activity, but few examples can be cited other than the well-known one of the hormone insulin. Although urease is a typical SH enzyme, extensive reduction of disulfide groups required for the maintenance of protein structure may result in inactivation (*15*). Clostridial collagenase apparently requires the SS bond and is inactivated by reducing agents (*16*).

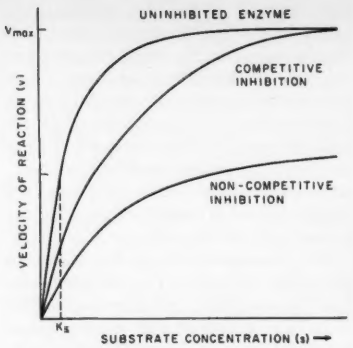


Fig. 3. The rate of the catalyzed reaction as a function of substrate concentration is plotted for an active enzyme and for an enzyme inhibited by either a competitive or a noncompetitive inhibitor (*34*).

Polypeptide chain. By no means all of the protein molecule is required for enzyme activity, and in many cases it has been possible to split the polypeptide chain without loss of enzyme activity. Mild conditions of hydrolysis must be used, however, and one is limited primarily to enzymes that split the peptide bond. Proteolytic enzymes as well as amino- and carboxy-peptidases have furnished evidence that in many cases amino acids and peptides can be successively removed from the polypeptide chain of an enzyme before loss in activity occurs. For example, carboxypeptidase can remove 20 percent of the nitrogen of ribonuclease while more than 70 percent of the enzyme activity is retained (see *14*). Although glyceraldehyde-3-phosphate dehydrogenase is inactivated by proteolytic enzymes, its activity is restored by SH compounds (*14*). Pepsin can be partially self-hydrolyzed and retain activity.

Phosphate. Certain proteins contain phosphate (attached to the hydroxyl group of serine) that can be readily removed (*17*). In the case of phosphorylase, the removal of phosphate by phosphatase results in complete loss of activity. This inactivation can be reversed by dephosphophosphorylase kinase and adenosine triphosphate. Glucagon and epinephrine may play an indirect role in this reactivation (*18*).

Metals. Metals may be firmly bound in stoichiometric proportions to proteins (metalloenzymes) or loosely and nonspecifically bound to proteins (metal-enzyme complexes) (*19*). Included in

the first category are copper, iron, molybdenum, and zinc, all of which are located in the active site of most oxidative (also hydrolytic in the case of zinc) enzymes. Agents with high affinity for the metal and suitable steric configuration completely inhibit the enzyme by formation of a metal-inhibitor complex. Inhibitors that have been especially useful in elucidating the structure of metalloenzymes are cyanide, azide, carbon monoxide, hydrogen sulfide, phenylthiourea, *o*-phenanthroline, 8-hydroxyquinoline, and ethylenediamine tetraacetic acid. If the inhibitor has not separated the metal from the protein, the enzyme can often be reactivated by suitable removal of the inhibitor (*19*).

Loosely bound metal ions that activate enzymes by forming metal-enzyme complexes include magnesium, manganese, potassium, calcium, iron, and cobalt. Metal ions that activate enzymes can be readily removed from the system by dialysis, by chelating agents such as citrate, oxalate, pyrophosphate, and Versene, or by reagents specific for a particular metal. Fluoride is especially useful as an inhibitor of magnesium-activated enzymes such as enolase. Competition among metal ions may occur for the reactive groups of the enzyme; for example, cobalt, copper, and zinc may inhibit the activation of prolidase by manganese; silver and mercury inhibit the activation of arginase by cobalt and manganese; and sodium may interfere with potassium in its activation of glycolysis. The problem of metal ions is complicated by the fact that these cations may also complex with the substrate, thereby facilitating or inhibiting enzyme action (*19*).

Coenzymes. Enzyme systems that require a coenzyme may be inhibited by reagents which combine with the coenzyme either before or after its removal from the protein apoenzyme. Especially illuminating have been studies on the substitution for the coenzyme of a compound (anticoenzyme) that resembles the structure of the coenzyme sufficiently closely so that the anticoenzyme displaces the true coenzyme from the apoenzyme. Since the essential group of the coenzyme is usually one of the B vitamins, most of the anticoenzymes fall into the category of antivitamins. Not only can the antivitamin act as a competitive inhibitor in an enzyme system requiring a coenzyme, but in the living cell it may also block the synthesis of the coenzyme itself, causing the organism to develop symptoms of a vitamin deficiency (*20*).

Coenzymes that can be blocked by antivitamins include the pyridine nucleotides, flavin nucleotides, thiamin pyrophosphate, pyridoxal phosphate, coenzyme A, *d*-lipoic acid (6,8-dithiooctanoic acid), and many others. Specificity among the coenzymes is extreme, for example *l*-lipoic acid inhibits the functioning of the coenzyme as do also the analogous 4,8- and 5,8-dithiol acids. Similarly in the case of the pyridine nucleotides, reduction involves the introduction of hydrogen into either the cis or the trans configuration of the para position of the nicotinamide (*21*). From these studies it is clear that only minor alterations in a vitamin molecule may convert it into an antivitamin capable of blocking directly or indirectly the functioning of a coenzyme in an enzyme system. Enzymes containing both coenzyme and metal can be inhibited by reagents for the metal as well as by anticoenzymes.

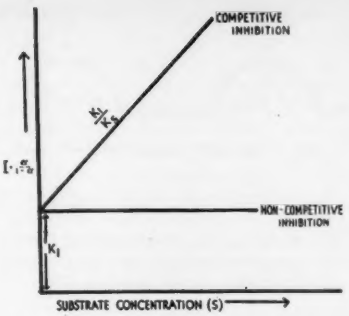


Fig. 4. Inhibitor concentration multiplied by the ratio of inhibited enzyme to active enzyme is plotted as a function of substrate concentration for both competitive and noncompetitive inhibition (*34*).

Architecture of the Active Site

While previously discussed inhibitors of selected groups have contributed greatly to knowledge of the active site, more direct information has come from studies specifically directed toward that part of the enzyme molecule directly concerned in catalysis. Competitive inhibitors that bear a direct or indirect relationship to the natural substrate have been especially useful. Since such inhibitors interfere with the metabolism of normally occurring compounds, they are called antimetabolites. Also included in this category are the antivitamins, which have already been discussed. Although the antimetabolites are invaluable in mapping out the topography and chemical nature of the reactive group, their contributions to our knowledge of intermediary metabolism, including the citric acid and the urea cycles and biosynthesis in general, are equally significant. Applications to applied problems, especially in agriculture, medicine, pharmacology, dentistry, and nutrition, are developing rapidly and promise exciting vistas for the future.

Use of homologous series of compounds has furnished information on the dimensions of the active site. The introduction of one CH_2 group into an inhibitor may greatly alter its action, suggesting that steric configuration of the active site is highly specific. Increase in size by only a few angstrom units may convert an inhibitor into a molecule that no longer has access to the enzymatic site. This is well illustrated by the alcohol dehydrogenase system. The length of the aliphatic chain determines whether the alcohol is a good or poor substrate, an inhibitor, or without effect on the enzyme (*22*).

One of the best examples of inhibition analysis by the use of antimetabolites is given by studies of Nachmansohn, Wilson, and their collaborators (*11, 23*) on acetylcholinesterase. This enzyme is strongly and irreversibly inhibited by certain chemical warfare agents and insecticides belonging to the group of phosphate esters, including tetra-alkyl pyrophosphates, dialkyl *p*-nitrophenyl phosphates, and dialkyl fluorophosphates. The lethal action of these nerve gases is due to an inhibition of acetylcholinesterase which is not reversed by dialysis. These inhibitors phosphorylate a basic group (imidazole ?) of the active esteratic subsite which is normally bound to the ester function of acetylcholine and is involved in the catalytic hydrolysis of the ester linkage. Similar inhibitor studies using antimetabolite analogs of acetylcholine have shown that the active site of the esterase consists of a second subsite, called the anionic site, capable of binding and orienting, by Coulombic and van der Waals' forces, ammonium structures and responsible for binding the choline part of the acetylcholine (see Fig. 6). In addition to inhibition by choline analogs, the esterase is inhibited reversibly at lev-

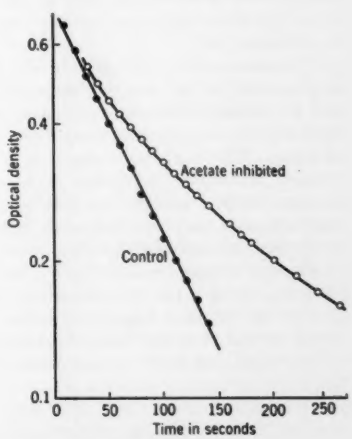


Fig. 5. Catalysis of H_2O_2 decomposition by beef-liver catalase in the presence and absence of 0.3*M* sodium acetate in 0.1*M* phosphate buffer, *p*H 6.0 at 25°C; 10^{-8} to 10^{-5}*M* H_2O_2 (*36*).

els of $10^{-6}M$ by such powerful alkaloid drugs as eserine, prostigmine, atropine, and curare (*23*).

In the case of the alkyl phosphate-enzyme complex, the inhibition is ordinarily irreversible, since reaction with water to regenerate unbound active enzyme is extremely slow. Some reactivation was obtained with nucleophilic reagents such as hydroxyamine and pyridine, which compete with the dialkylphosphoryl group for the positively charged esteratic site. Far more effective in reactivation were compounds that in addition possessed a cationic center for Coulombic binding to the anionic site. Included in this group of reactivators are nicotinohydroxamic acid and 2-pyridine aldoxime methiodide. The latter compound has been used successfully as an antidote to nerve-gas poisoning and is capable of repairing the chemical lesion produced by the alkyl pyrophosphate (*24*).

Inhibition in Living Systems

Enzyme inhibitors have profound effects on living organisms by blocking vital reactions of intermediary metabolism. In this way, they may modify the behavior of the cell or organism, affect growth, development, and reproduction, and produce necrosis and death. Interpretation of inhibition is fraught with difficulties because it does not necessarily follow that the locus of action is a particular enzyme system from the fact that an inhibition *in vitro* can be demonstrated. It must be proved that the enzyme under indictment is actually inhibited in the living system at the concentration of inhibitor that is known to have accumulated inside the cell. In addition, the enzyme block must quantitatively explain the biological effect of the inhibitor (*25*).

An example of the difficulties involved is presented by the nitrogen mustards, which have been widely used with partial success in the treatment of certain types of cancer. These cytotoxic materials inactivate hexokinase, adenosine triphosphatase, choline oxidase, esterase, and acetylase, and they interfere with biosynthesis. The explanation of the mode of action of nitrogen mustards is not this obvious, however, for the concentration of the drug required for enzyme inhibition is greater than that found in tissues after a lethal dose has been administered (*26*).

Except in the case of chemical warfare, the biochemist would like to use an enzyme inhibitor like a surgeon's scalpel to differentiate at the molecular level between closely related living systems. In theory, the difference between them may be subtle indeed and need involve only

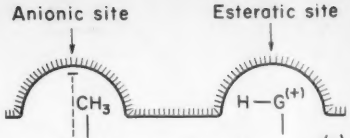


Fig. 6. Schematic presentation of interaction between the active groups of acetylcholinesterase and its substrate (*23*).

one enzyme in a thousand or more; in such a situation, a specific inhibitor might be able to eliminate one of a pair of cells or organisms. While such differential and specific effects of inhibitors do indeed depend on quantitative or qualitative differences in enzymes associated with alternate pathways of metabolism that exist between pathological and normal tissues or between host and parasite, other properties may be equally important. In particular, permeability differences involving cell wall, plasma, nuclear membranes, and mitochondrial membranes (both external and in the christae mitochondriales) are of critical importance in explaining the difference in susceptibility to such biologically active compounds as drugs, antibiotics, and chemotherapeutic agents.

Inhibition analysis of cell chemistry. The first use of inhibitors in living systems was as blocking agents in unraveling the successive steps in glycolysis, in the citric acid and urea cycles, and in numerous systems of biosynthesis. A recent addition to the list, which includes such famous inhibitors as iodoacetate, fluoride, and malonate, is fluoroacetic acid, a poison from certain South African plants. In man a "lethal synthesis" of fluorocitrate from fluoroacetate occurs which blocks the citric acid cycle by an inhibition of aconitase (*27*). Inhibition analysis was not only instrumental in elucidating metabolic pathways, but these investigations in turn have validated the theory of enzyme inhibition as applied to living matter.

Antimicrobial enzyme inhibitors. Studies on the use of inhibitors as bactericides and fungicides have proceeded at a rapid pace ever since sulfanilamide proved to be a competitive inhibitor that blocks the utilization of *p*-aminobenzoic acid in the synthesis of the folic acid enzymes. Gould *et al.* (*28*) found that bisphenolic compounds such as hexachlorophene strongly inhibit succinoxidase, cytochrome oxidase, and lactic dehydrogenase, but it is not clear that this accounts completely for the bactericidal action of hexachlorophene. Penicillin blocks both protein and nucleic acid metabolism by inhibition of peptide bond synthesis, oxidation of nucleotides, and their formation from purines (*25*). Streptomycin is a nonspecific inhibitor with a marked effect on diamineoxidase. It also interferes with the oxidation of pyruvate and oxalacetate.

Bacteria are more susceptible than mammals, apparently because of the relative impermeability of plasma membrane and mitochondria of the animal cell to streptomycin (see *25*). Chloramphenicol is structurally related to phenylalanine and may inhibit its incorporation into proteins. Its antibiotic properties might be related to its ability to block protein synthesis in bacteria. Antimycin is a powerful inhibitor of succinoxidase. Tetracycline uncouples respiration from aerobic phosphorylation (*29*). This antibiotic action may be prevented by magnesium, which binds the tetracycline. These few examples were chosen to indicate the usefulness of the hypothesis that antimicrobial agents can act as enzyme inhibitors.

Drugs as enzyme inhibitors. The concept that the pharmacological action of drugs may be the result of their inhibition of enzyme systems has proved fruitful and now affords a rationale in the search for chemicals with physiological action. Drugs previously discussed, which inhibit acetylcholinesterase, constitute one of the best documented examples in this category. Acetazoleamide (Diamox), which is useful in the treatment of edema, glycoma, and epilepsy, reversibly inhibits carbonic anhydrase even at concentrations of $10^{-8}M$. By interfering with this enzyme in mammals, Diamox prevents a tissue (kidney, stomach, brain, pancreas, and ciliary bodies) from secreting acid or base (*25*). Disulfiram (Antabuse), which is useful in the treatment of alcoholism, apparently inhibits enzymes that oxidize acetaldehyde. Hence disulfiram causes an accumulation of toxic aldehyde after alcohol is administered. This drug has been shown to inhibit copper and SH enzymes (*25*).

Anesthetics and hypnotics produce a decrease in nerve activity accompanied by a slight decrease or increase in oxidation and an interference with the utilization of adenosinetriphosphate. These drugs appear to affect most markedly the stimulated respiration and synthesis of phosphate bond energy of active as contrasted with resting nervous tissue (*30*). In the respiratory chain of the cell, enzymes operating between the pyridine nucleotides and cytochrome *b* constitute the links most susceptible to inhibition by hypnotics and narcotics. Although an encouraging beginning has been made on the mode of action of drugs, much research remains to be done before their action can be explained in terms of enzyme inhibition.

Inhibitors in cancer chemotherapy.

The search for inhibitors that distinguish between enzymes of normal and neoplastic cells has not been easy in view of the general similarity of the metabolism of the two types. Most effective in the treatment of cancer have been antimetabolites that interfere with either folic acid enzymes or enzymes involved in nucleic acid biosynthesis, or both. The most effective folic acid antagonists are the 4-amino derivatives of folic acid, aminopterin and α-methopterin, which prevent the conversion of folic acid to folinic acid (citrovorum factor). In this way, folic acid is prevented from acting as a formylating agent in biochemical one-carbon transfer reactions. Folic acid antagonists are especially useful in the treatment of acute lymphoblastic leukemia (*31*). The purine antagonists include 6-mercaptopurine, azaguanine, 2,6-diaminopurine, thioguanine, 6-chloropurine, and the pyrazolo pyrimidines.

A more specific attack on blocking purine metabolism has been made possible by the work of Buchanan and associates (*32*), who have characterized the enzymes and elucidated each step in the biosynthesis of purines. The antibiotics, azaserine and 6-diazo-5-oxy-L-norlucine (DON) are structural analogs of glutamine and block the enzyme that utilizes it in purine synthesis. The ability of these antibiotics to block the synthesis of nucleotides is quantitatively related to their blockading of the growth of certain types of neoplasms (*33*). Many other types of enzyme inhibitors are being investigated for possible use in cancer chemotherapy.

Summary

The use of chemical reagents as enzyme inhibitors has yielded information concerning the mechanism of inhibition and the role in catalysis played by active groups on the protein apoenzyme, the coenzyme, or the metal component. Inhibition analysis has also furnished valuable clues concerning the architecture, chemical properties, and catalytic mechanism of the active site of the enzyme. In many cases, *in vivo* effects of inhibitors can be closely correlated with *in vitro* inhibition of purified enzyme systems. The effects of antimicrobial and anticancer agents, insecticides, and drugs can often be explained in terms of enzyme inhibition. The design and synthesis of new inhibitors offers great promise when applied to the control of undesirable organisms and to the prevention and cure of disease in the immediate future.

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J. W. Scott, Zoologist

John W. Scott was born on a farm in Lewis County, Missouri, on 1 July 1871. From the local schools he went on to graduate from the University of Missouri and later received a master's degree in psychology at the same institution. After some experience in high-school teaching he came to a major decision: he wanted to learn all that there was to know about some field of science, and he chose zoology. In taking his Ph.D. at the University of Chicago and throughout the rest of his life he was keenly interested in all branches of animal science. He could truly be called a general zoologist.

In 1913 he was appointed chairman of the department of zoology at the University of Wyoming, and his subsequent scientific interests were centered around this state and institution. He once said that he was determined to master any subject that he undertook, and he set about learning all that there was to know about Wyoming. For 40 years he walked, rode, and drove over every corner of the state, collecting, photographing and observing. With this knowledge, he helped lay the foundation for the study of animal ecology in the area, and he summarized it in a chapter in Shelford's *Naturalist's Guide to the Americas*.

To master meant to understand, and his understanding of nature included affection. In his spare time he was an ardent fisherman, and he soon became an ardent conservationist. As president of the state Izaak Walton League, he worked for the adoption of a model fish and game law and was later asked to help put it into effect as executive secretary of the State Fish and Game Commission. He was made an honorary national president of the Izaak Walton League and served as chairman for its Conservation Education Committee, which became the present Conservation Education Association, of which he was also honorary president.

His early scientific work was concerned with the embryology of the marine annelids which he studied at the Woods Hole Marine Biological Laboratory, where he was an instructor in the

invertebrate course for several years. However, his major research interest soon changed to parasitology. Beginning at the Kansas State Agricultural College and later as research parasitologist at the Agricultural Experiment Station of the University of Wyoming, he at first concerned himself with parasites of livestock, demonstrating the insect transmission of swamp fever in horses and working extensively with *Sarcocystis tenella* of sheep. Later he became interested in the parasites of wildlife, particularly the tapeworms of the genus *Diphyllobothrium* and the coccidian parasites of the sage grouse. Working out the life-cycle of the latter led to the first description of the mating behavior of the sage grouse, the discovery of one of the highest degrees of social organization in gallinaceous birds, and a comparative behavioral study of two related species. At the time of his death he was working on two problems: one on the relationships between *Diphyllobothrium cordiceps* and *D. latum,* which he concluded were physiologically and morphologically distinct, and the other on the races of *Eimeria* in the sage grouse, which developed in isolation conforming to the isolation produced by the social behavior of the host.

As a teacher, Scott had a gift for presenting a clear organization of a subject, but his outstanding capacity was for friendships. He was an idealist in human affairs and could understand and appreciate any quality except selfishness. Those whom he inspired share his belief that the pursuit of knowledge is an honorable occupation whose end is general and individual welfare. He died on 15 August 1956 in Laramie, Wyoming.

J. P. Scott
Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine

News of Science

AAAS Awards

The following awards were presented during the recent AAAS annual meeting in New York.

The AAAS-Anne Frankel Rosenthal memorial award went to Jacob Furth, associate director of research at the Children's Cancer Research Foundation, Harvard Medical School. The award, consisting of $1000, is from funds provided by the Rosenthal Foundation.

Furth was born in Hungary and educated in Germany, where he began his professional career. He came to the United States in 1924. After a year on the staff of the Henry Phipps Institute in Pennsylvania, he was appointed to the faculty of Cornell University College of Medicine, where he remained until 1948. Then for the 4 years he served as chief of the pathology and physiology section of the Biology Division of the Oak Ridge National Laboratory. In 1954 he was appointed to his present position at Harvard.

Herbert C. Kelman, research psychologist at the National Institute of Mental Health, received the $1000 AAAS Socio-Psychological Research award. Kelman was born in Vienna 29 years ago. Following receipt of a Ph.D. degree from Yale University in 1951, he was given a fellowship by the Social Science Research Council and spent a year at the Phipps Psychiatric Clinic of Johns Hopkins University. From 1952 to 1954 he served as a U.S. Public Health Service research fellow. Then, after a year at the Center for Advanced Study in the Behavioral Sciences at Stanford, Calif., he assumed his present position.

Kelman's prize winning study was a theoretical and experimental investigation of social influence. Social influence or social pressure sometimes leads a person to change his attitudes or behavior, but this conformity takes place at different levels. A person may conform because he expects to be rewarded for conforming and punished for nonconforming behavior. He may conform because he wants to maintain good relations with other people whose behavior or attitude he copies. Or, he may conform because he really believes that the ideas or actions are good and proper. Kelman analyzed and studied experimentally some of the factors involved in these three kinds of compliance with social influences. Kelman was a college roommate of Yehudi A. Cohen of the Albert Einstein College of Medicine who received the award last year.

The AAAS-Ida B. Gould memorial award for research on cardiovascular problems was presented jointly to C. W. Lillehei of the University of Minnesota School of Medicine and his associate Richard Allison DeWall. The award is being given for Lillehei's leadership in the field of open heart surgery through the preparation of oxygenators of various sorts, including the pump oxygenator that was originated by DeWall.

Neal E. Miller, James Rowland Angell professor of psychology at Yale University, and James Olds, associate research psychologist in the department of anatomy at the University of California, Los Angeles, received the 29th Newcomb Cleveland $1000 award for their experiments with animals which show that certain areas in the brain apparently govern feelings of punishment and gratification. The prize-winning papers were "Learning and performance motivated by direct stimulation of the brain," by Miller, and "Effects of hunger, sex, and tranquilizers on localized reward systems in the brain," by Olds.

Miller and his colleagues at Yale have shown how different emotions and drives may be aroused by stimulating certain places deep in a primitive part of the brains of rats and other animals. They have studied reactions that seem to be like pain and fear, flight, rage, hunger, sex, and thirst. Olds, working with Milner in Montreal, discovered that electric stimulation of other points deep in the brain can act as a reward. Thus, while the animals used by the Yale group would work to escape direct stimulation of the brain, Olds' rats would work to get it. Since Olds found that his reward effect could be influenced by drives, he could use it as a means of studying the location of various "drive centers" in the brain. The work going on in the Yale and California laboratories and that in other laboratories is fitting together to begin to give a picture of how motivations are aroused deep in the brain.

Population Changes

Families are becoming larger in the United States, the Metropolitan Life Insurance Company's statisticians report. An increasing number of couples are now having a third or fourth child. The annual rate for third births has climbed from 1.8 per 100 married women under age 45 in 1940–41 to 3.1 per 100 in 1954–55. For fourth births, the rate in-

creased by 70 percent during this period. Fifth and subsequent births have also increased somewhat in recent years and are likely to continue upward for the balance of the decade, although there is little likelihood that the rates for these birth orders will return to the levels of the 1920's.

Second births increased almost without interruption from a low point in 1933 to a peak in 1952. Although the rate has fallen off somewhat, it still is at an unusually high level—one-third above the rate in 1940, and about one-eighth higher than in 1920. In 1945–55 the number of families that had a second child exceeded those that had a first child—a situation which is probably without precedent in our history.

At the other end of the scale, the Metropolitan Life Insurance Company statisticians report that the proportion of older people has been increasing for more than a century, slowly at first and more rapidly in recent decades. The proportion of population at age 65 or older is 8.6 percent, or about one in 12. In 1900 only 4.1 percent of all Americans were in this age group.

According to the Population Reference Bureau, Inc., for the third consecutive year the number of births in the US has totaled more than 4 million. This rising tide of births will soon add further to the mounting school enrollment figures. For the three years from October 1953 through October 1956, kindergartens and elementary schools had to expand enough to take in an extra million children each year. The Census Bureau finds that the total increase for those three years was 3,119,000. The big increase in school children is still to come. Kindergarten enrollment went up 82 percent from 1950 to 1955. Between 1950 and 1955, the number of children who are 5 years of age or under jumped from 14,184,504 in 1950 to 18,305,000 in 1956, an increase of 4,120,496. The number of children in elementary schools increased by 24 percent, and high-school enrollment rose only 19 percent.

Uranium Production

The Atomic Energy Commission has disclosed for the first time statistics concerning uranium ore reserves and uranium mining and milling operations. The information, which was limited to production since 1 July 1955, was authorized by the commission's revised declassification guide.

The uranium ore reserves still in the ground on 1 Nov. 1956 were estimated in millions of tons as follows: New Mexico, 41; Utah, 7.5; Colorado, 4.1; Arizona, 2.6; Wyoming, 2.3; Washington, 1.5; and others, 1. The total is 60 million tons.

The uranium ore mined during the period from July to December 1955 was 840,000 dry tons; from January to June 1956, 1.34 million dry tons; and from July to December 1956, 1.66 million dry tons.

The amount of uranium concentrate milled from the raw ore doubled this last year, the yield of concentrate from the crude ore averaging about ¼ of 1 percent. At the beginning of 1956, uranium concentrate was produced at a rate of about 4000 tons per year; at the close of the year the rate was more than 8000 tons per year. Specifically, uranium concentrate milled during the period from July to December 1955 was 1600 tons; from January to June 1956, 2600 tons; and from July to December 1956, 3400 tons.

At present, 12 uranium mills are in operation in the United States. All are privately owned with the exception of one AEC-owned plant. The total private investment is established at $50 million, with a total daily capacity of 8960 tons. Eight more mills, representing an investment of about $35 million and a rated daily capacity of 4025 tons, are scheduled for completion in 1957 or early 1958.

Randomized Cloud-Seeding Experiment

A recent decision of the Board of Supervisors of Santa Barbara County, Santa Barbara, Calif., to finance a randomized cloud-seeding experiment provides an unusual opportunity for studying the effects of silver iodide smoke, produced by ground generators, on storms passing over mountainous areas. It appears that this will be the first randomized experiment conducted in the United States using ground generators of silver iodide. Also, because of possible complications with lawsuits for damages and the consequent reluctance of public agencies to conduct cloud-seeding experiments on their own, it may be quite some time before another experiment of this kind is organized. In the past there appear to have been only two randomized cloud-seeding trials, those conducted by the U.S. Weather Bureau and by the University of Chicago meteorologists and statisticians. However, these trials involved seeding from aircraft.

During the decade that has elapsed since the discovery of techniques for artificially nucleating supercooled clouds there has been a large amount of effort expended to secure an answer to the question, "Does cloud seeding produce significant increases in precipitation?"

Several years ago the Division of Water Resources of the Department of Public Works of the state of California conducted an investigation of this subject, particularly in relation to the widespread commercial cloud-seeding operations in California. With the help of the Statistical Laboratory of the University of California, it was established that no clear-cut answer to the question of the efficacy of the cloud-seeding operation is available and that none can be expected until a special, so-called "randomized," experiment is performed.

In order to understand this pessimistic conclusion one must take into account that, according to the opinion of professional meteorologists, not all storms are suitable for seeding and only a part of them are actually seeded. Also, in order to judge whether or not the seeding is effective, one must have some sort of standard of comparison, such as, for example, the amount of rain fallen from the same storm in a comparison area, presumably not affected by seeding. In these conditions, even if the comparison between the rain in the target and in the comparison areas appears favorable to the conclusion that seeding is beneficial, there is always the question of whether or not the observed excess of rain in the target is the effect of seeding or a mark of success of forecasting.

In fact, the meteorologist engaged in cloud seeding may be expected to be able to identify among the approaching storms those that will deposit in the target relatively more rain than the others. Then, if only those more promising storms are seeded, the comparison with any preassigned standard would tend to indicate a positive effect of seeding, even though the actual effect of this operation is minute or nil.

This difficulty of distinguishing between the success of forecasting and the success of seeding can be avoided by performing a randomized trial. The meteorologist engaged in weather modification is allowed to select at will the opportunities for seeding. Once such an opportunity is identified, a random experiment is performed: for example, a coin is tossed. If the coin falls heads then the actual cloud seeding begins, but not otherwise. However, the observations of the rainfall are conducted on all seeding opportunities, both those seeded and those not seeded. Then, with a sufficiently long series of observations, the comparison between the seeded and not seeded storms allows a definite conclusion regarding the effectiveness of seeding as such, free from the possible effects of forecasting.

For quite some time appeals for a randomized experiment went unheeded. On the one hand, the communities that paid for cloud seeding (and they were those that believed in the effectiveness of these operations) were reluctant to let about one-half of the seeding opportuni-

ties go unseeded. On the other hand, the companies engaged in commercial cloud seeding did not show any enthusiasm for a randomized trial.

This impasse was broken last May at a conference at the Statistical Laboratory of the University of California at which the problem of artificial weather modification was publicly discussed. After several papers were presented to the audience, all emphasizing the advantages of a randomized experiment, Robert D. Elliott, president of the North American Weather Consultants, took the floor and announced that, provided that financial arrangements could be made, his company would be prepared to submit to a randomized cloud-seeding experiment.

For some years past Elliott's company has been engaged in cloud-seeding operations in Santa Barbara County under contract with the county. Last summer this contract was considered for renewal, and Elliott was successful in persuading the Board of Supervisors of the county to agree that the operations over the forthcoming 3 years 1957–59 be conducted on a randomized basis. At its September meeting the Board of Supervisors approved the contract, and the randomized experiment is to begin on 1 Jan. 1957.

As conceived now, the Santa Barbara experiment will be a cooperative enterprise. With financial support of Santa Barbara County, the actual cloud seeding will be performed by the North American Weather Consultants. The California State Department of Water Resources has undertaken the responsibility of collecting the data on the rainfall. This activity, with Robin R. Reynolds in charge, involves installing and servicing a considerable number of rain gages over the target and over the three selected comparison areas. These rain gages, 38 of which are automatic, are being lent by the U.S. Weather Bureau. The local Forest Service is interested in the experiment and is expected to be very helpful in the observational part of the program. Finally, the Statistical Laboratory of the University of California, Berkeley, has designed the experiment and will evaluate the results.

It is hoped that the expenditures connected with these activities will be covered by a grant from the National Science Foundation. In the meantime, the Office of Naval Research has authorized the Statistical Laboratory to meet the initial expenses connected with the trial from its grant to the Statistical Laboratory intended for other purposes.

While the purely practical question of effectiveness of commercial cloud seeding, with the use of ground generators, is likely to be settled after the 3 years of the proposed study, the framework of the experiment just described would leave unanswered a host of important theoretical questions. The outcome of the experiment may be favorable or unfavorable. In either case there will be questions on why the results were as they were, what was the mechanism of success or failure, did the seeding affect equally all the storms passing over Santa Barbara County, and so forth. It will be realized that, given the necessary observations, the randomized design of the experiment will provide an opportunity for clarifying many problems of this kind.

With this in mind the President's Advisory Committee on Weather Control decided to use the Santa Barbara experiment for certain additional radar observations, not originally contemplated. However, there is little doubt that much more can be done in this same direction.

On 4 Dec. a conference was held in the Statistical Laboratory to consider the opportunities offered by the Santa Barbara project. In addition to Robin R. Reynolds of the California State Department of Water Resources, R. D. Elliott of the North American Weather Consultants, and the hosts at the Statistical Laboratory, this conference was attended by James E. McDonald of the Institute of Atmospheric Physics of the University of Arizona and Walter S. Hopkins and Arnold Court of the California Forest and Range Experiment Station.

At this conference the prevailing opinion was that the opportunities provided by the Santa Barbara experiment should be exploited to the utmost. As a consequence, it was decided to make public the existing arrangements with the hope that individuals, agencies, and institutions interested in artificial weather modification might undertake various observational programs in addition to those already planned. The following particular points were raised.

1) *Two independent sets of observations of precipitation.* In order to avoid any possible doubts about the reliability of records of rain in the target and in the comparison areas, it is desirable to have for analysis two independent sets of observations. Thus, some of the rain gages now available could be installed and serviced by the California State Department of Water Resources, as originally planned. The remaining rain gages could be entrusted to a recognized scientific institution that would undertake responsibility for installing them in the target and in the comparison areas and for servicing them in order to obtain a set of observations independent of those of the Department of Water Resources.

2) *Radar observations.* The aid of President Eisenhower's Advisory Committee on Weather Control has already been promised in providing radar observations using an APS-15 3-centimeter radar to be located on the summit of La Cumbre peak in the Santa Ynez Mountains. There is need for a vertical-pointing cloud-base-and-top indicating radar located somewhere on the coastal plain near Santa Barbara to give a continuous record of the cloud structure of the storms moving into the target area from the Pacific. Special interest centers around the question of generating cells and small convective elements imbedded in the storm cloud systems, for experience in other areas indicates that these elements may be the chief natural units for release of precipitation from frontal-cyclonic storms. A much more illuminating analysis of the target and control rainfall data will become possible if such a radar could be made available.

3) *Freezing nuclei observations.* Inasmuch as there is virtually no observational data on natural freezing nuclei counts prevailing during seeding experiments that have been carried out in the past, and inasmuch as the entire rationale of silver iodide seeding is based on the premise that a deficit of freezing nuclei exists in certain places and at certain times, it follows that a properly planned experiment should include nuclei counts. It is hoped that some agency or institution can offer assistance leading to provision of such counts during the Santa Barbara trials.

Ideally, counts should be made upwind of the generators and also downwind in the silver iodide plumes. It is desirable to measure nuclei at least at sea level on the Santa Barbara coastal plain upwind from all generators and, if possible, also on the summit of the Santa Ynez range. Identical nuclei counters are desirable in the latter case, but counts of any kind, in the face of current paucity of knowledge concerning nuclei, will be of substantial aid to the over-all experiment.

4) *Airflow observations.* Among the current uncertainties in the cloud-seeding problem are those concerned with the details of movement of nuclei from generator to cloud. During an experiment of the type to be started in Santa Barbara in 1957, there is compelling need to perform all possible experiments aimed at defining the trajectories of the nuclei in order to state which parts of passing storms have been seeded and which have been unaffected by ground-released nuclei. Three means of securing this kind of information suggest themselves. They are not all of equal feasibility.

As a minimum, a series of zero-lift pilot balloon runs should be made during a number of seeded situations. These will give some insight into the paths followed by nuclei from ground at least up to cloud base level and will reveal the effects of the first main orographic barrier encountered by the nuclei.

Second, the more complete information obtainable by using tracer techniques, such as those employing fluores-

cent zinc sulfide and aircraft impactor equipment, should be added if at all possible. These give information as to particle concentrations downwind from the generator, and concentrations are of key interest in assessing the numbers of ice crystals per unit volume of seeded storms.

Third, actual counts of silver iodide nuclei in the plumes emitted by the generators should be carried out if it becomes possible to obtain airborne nucleicounting equipment. It is recognized that cloud base heights and general storminess during seeding situations, plus the hazard of the mountains themselves, pose serious problems here, but the need is a very real one.

5) *Synoptic analysis.* Meteorologists familiar with past seeding trials will recognize the need for much more thorough synoptic analysis of the storms seeded during any given program. In the Santa Barbara experiments there is need for some institution or agency to undertake the analysis of the Pacific frontal-cyclonic systems that comprise the seeded population, in order to gain badly needed physical insight into the reasons for the statistical answers that may be forthcoming. Whether the final answers prove positive or negative there will be great scientific interest in the detailed processes that are involved in the seeded storms of this experiment. Thermodynamic analyses and airflow analyses are needed. Fortunately, it is in the nature of this problem, that the analysis can be done later, without any immediate provision of additional facilities. However, the interest of other groups in attacking this problem is invited now.

Inquiries regarding the Santa Barbara Cloud Seeding Experiment should be addressed to either of the present three participating institutions, preferably with copies to the remaining two, as follows: (i) California State Department of Water Resources, Sacramento, Calif.: Attention Mr. Robin R. Reynolds; (ii) North American Weather Consultants, Santa Barbara Municipal Airport, Santa Barbara, Calif.: Attention Mr. Robert D. Elliott; (iii) Statistical Laboratory, University of California, Berkeley 4, California: Attention Professors J. Neyman and E. L. Scott.

J. Neyman
Statistical Laboratory, University of California, Berkeley

Fertile Field for Communist Propaganda?

A federal judge has aroused the scientific community by commenting publicly that the younger generation of pure scientists seems to have succumbed to Communist propaganda. Alexander Holtzoff made this observation in Washington, D.C., when he sentenced Bernard Deutch, a graduate student in physics at the University of Pennsylvania, to 90 days in jail for contempt of Congress.

Deutch was a witness before the House Un-American Activities Committee at a hearing in Albany, N.Y., in April 1954. He admitted membership in a Communist group while attending Cornell University and answered questions about his personal activities. However, he refused on moral grounds to name other members of the group.

In November 1955 Federal Judge James R. Kirkland dismissed a contempt indictment against Deutch because it had failed to specify "willful" intent. However, the indictment was reinstated last July by the Federal Court of Appeals, which ruled that Deutch's refusal to answer had been a "positive, affirmative act" and "by its very nature deliberate and willful."

When Judge Holtzoff found Deutch guilty of these charges on 13 Dec., he addressed the court as follows:

"From evidence admitted in other cases that have come before the court, the court has gleaned the inference that the younger generation of pure scientists, specifically engaged in research in physics, has succumbed to Communistic propaganda."

He went on to explain that he was referring particularly to younger persons "engaged in pure science," and stated that a "dangerous" number of nuclear scientists have been found to be Communists. He said further that because of the brilliance of these scientists, they were potentially especially harmful "as subversive instruments." He then observed that "our educational methods have so changed in recent years" that young scientists lack "a proper cultural background" and are "abysmally ignorant of history, political science and economics." Deutch remains free on $500 bond pending an appeal.

So far two organizations have responded vigorously to Holtzoff. Charles C. Price, chairman of the Federation of American Scientists and head of the chemistry department at the University of Pennsylvania said in a letter that at least 1000 research physicists and teachers had been indicted by the jurist.

"While there have been instances of a few scientists, including physicists, whose thinking led to their association with the Communist cause at some time in their lives, we of the Federation strongly believe that the facts do not support your broad indictment of a whole generation of research physicists." Price added that Holtzoff's charges "poorly serve our national efforts to encourage young people to seek careers in science."

The Philosophical Society of Washington, an organization that is composed of 700 natural scientists, has also written a letter to Holtzoff. Malcolm C. Henderson, research professor of physics at Catholic University, was chairman of the committee that composed the communication, which included the following:

"We consider that not only is the distinction you draw between the alleged susceptibility to communistic propaganda of the 'pure' versus the 'applied' scientist a fallacious one, but that there is no evidence that young scientists of any sort are more susceptible to such propaganda than other groups of young people within the general population. . . . We feel that you have been guilty of generalizing from an exceedingly small sample, and one which has been given most undue weight in the public press. . . . The damage that such ill-advised statements as yours may do is to be found in the divisive effect that they have, setting off the scientist even further from the general public, which is only too ready to distrust and dislike the habit of thought of the scholar or scientist. . . . Anything that makes a career in science less attractive to our young people, or which influences their elders to advise against it, can but weaken the country in the long run."

Expanded Conservation Program

The United States Fish and Wildlife Service will develop a greatly broadened conservation program for fish and wildlife resources. The goals of the program are to solve problems of destructive drainage threatening marshes and wetlands for migratory waterfowl and to initiate a planned program of land acquisition to meet Federal and state needs in wildlife management.

As the result of legislation approved by the 84th Congress, the service now has the authority to undertake greatly expanded programs for commercial fisheries. The service is reviewing every possibility that will benefit the fishing industry. All this material will be used in developing the new program.

Additional Declassification

A large additional volume of technical information essential to the development of a civilian nuclear industry here and abroad is authorized for open publication under a 1956 revision of the Tripartite Declassification Guide. The United States, Great Britain, and Canada use this guide to determine what atomic energy information, jointly held, may be published and what information is to remain classified.

The information declassified by the new guide, now approved by the three nations, relates to all phases of nuclear power from ore recovery and fabrication of fuel elements to the design and opera-

tion of plants for the chemical recycling of spent fuel elements from civilian reactors. Of prime interest to American industry is the newly authorized declassification of information on civilian power reactors.

The major release of data on research reactors dates back to November 1950. Many categories of restricted data have been available to cleared individuals and organizations in this country under the Atomic Energy Commission's Civilian Access Permit Program. The latest action will permit publication of a large portion of that information which hitherto has been governed by access permits. For example, among the facilities that become declassified under the new guide is our first full-scale civilian nuclear power plant now nearing completion at Shippingport, near Pittsburgh, Pa.; also the experimental sodium reactor at Santa Susana, Calif.; and the second-stage homogeneous reactor at Oak Ridge, Tenn. However, the access permit program remains as an important aid to the continued integration of U.S. industry and management in the atomic energy program on a free competitive basis.

In addition, and clearly related to the reactor data which will become available, is the declassification of the technology of the manufacture of heavy water; final stages of the separation of zirconium and hafnium, two metals used in reactors, and the liquid thermal diffusion process of isotope separation, which may be used to make slightly enriched uranium fuel.

Of interest to our friends abroad, especially those now participating in the program of cooperation in peaceful uses of nuclear energy through bilateral agreements, is the fact that the United States can now effectively cooperate with other friendly nations on an unclassified basis for civil power purposes. This will greatly facilitate the conclusion of agreements for cooperation.

Uranium mining operators, underwriters and investors in the United States and in other uranium producing countries will benefit by the removal of all tripartite restrictions on the publication of statistics on over-all uranium ore reserves, and present and future ore concentrate production figures. The world uranium industry, which now represents a private investment of many millions of dollars, will be able to participate in planning for nuclear power development.

Putting a new declassification guide into effect does not declassify any documents. The releasable information becomes publicly available when reports, drawings, photographs, and so forth are reviewed and certified to be declassified under the new guide. The commission will move ahead rapidly in its review of classified information of interest to industry. The commission expects to institute shortly an accelerated review program similar to the one that examined more than 30,000 documents and reports early this year. Following this accelerated rate of review, publication will be encouraged, and the most useful of the declassified material should be available within 6 months or less.

The information to be released will provide a practical basis for enlarging and improving high-school, college and university curricula on nuclear science and engineering, and textbook publishers will be enabled to produce new, updated texts and general study aids on the applications of nuclear energy.

News Briefs

■ The American Foundation for Allergic Diseases has reported that, although more than 17 million people in the United States suffer from allergic diseases, not more than 1500 physicians are practicing in the field of allergy. Two recent survey's by the foundation indicate that little improvement in this shortage can be expected in the immediate future. The surveys, made possible by grants from the New York Community Trust, were concerned with both graduate and undergraduate medical education in the field of allergy.

■ The American Medical Association reports that, during the academic year 1955–56, 1573 women were studying medicine in the 76 approved 4-year medical schools in the United States. This is a 2.3-percent gain over the previous year.

The Woman's Medical College of Pennsylvania had the highest enrollment of any school—182. The medical schools of Columbia University and State University of New York each enrolled 40 or more women.

■ More than 100 geologists, biologists, oceanographers, and other scientists have participated in the preparation of the Geological Society of America's *Treatise on Marine Ecology and Paleoecology*. Volume 2, *Paleoecology*, edited by Harry S. Ladd, will be available in January or February 1957. Advance orders may be placed with the Geological Society, 419 West 117 St., New York, N.Y.

Volume 1, edited by Joel Hedgpeth, will be published later in 1957.

■ The Department of Agriculture has reported that the total production of crops in the United States during 1956 was 6 percent above the average for the base period of 1947–49. This production, which equals the record of 1948 and 1955, was attained despite the reduced number of acres in cultivation and the losses due to a late spring and widespread drouth. The harvest was derived from 314 million acres, or some 29 million fewer acres than the average for the decade of 1945–54. The increase is attributed to the intensive use of farm machinery and fertilizer. The average yield per acre for 1956 was 123 percent of the average for 1947–48.

Scientists in the News

JAMES C. THOMSON, until recently medical consultant of the World Health Organization in Iran and Pakistan, has accepted a joint assignment under both WHO and the Food and Agriculture Organization to make nutritional status assessment surveys of the school children of Turkey. His address is UNTAB Office, P.K. 407, Ankara, Turkey.

CHARLES KITTEL, professor of physics at the University of California in Berkeley, has received the 1957 Oliver Buckley solid-state physics prize of the American Physical Society, for his applications of magnetic resonance methods to investigations of the electronic structure of solids. This $1000 prize is presented by the society "to a person who has been adjudged to have made a most important contribution to the advancement of knowledge in solid-state physics within the 5 years immediately preceding the award." The award will be presented at the annual meeting of the American Physical Society in New York at the end of January 1957, at which time Kittel will give the Buckley lecture on the subject "The role of magnetic resonance studies in the physics of solids."

THEODORE BERLAND, former assistant director of public relations at the Michael Reese Hospital Medical Center, Chicago, Ill., has joined the office of public relations of the University of Chicago as science writer. He succeeds GEORG MANN, who resigned to take another position.

The two A. Cressy Morrison prizes in natural science, which are awarded annually by the New York Academy of Sciences for original research, were presented to WILLIAM LOW, Enrico Fermi Institute for Nuclear Studies, University of Chicago, for his paper on "The paramagnetic resonance and optical spectra of some ions in cubic crystalline fields," and to GUY-LAURENT REMILLARD, Université de Montreal, Montreal, Canada, for his paper entitled "Histochemical and microchemical observations on the lipids of interscapular brown fat of the female vespertilionid bat."

Sir ARNOLD HALL, technical director and scientific adviser and consultant for the Hawker Siddeley Group, Ltd., London, England, delivered the 1956 Wright Brothers lecture of the Institute of the Aeronautical Sciences on 17 Dec. in the U.S. Chamber of Commerce Building, Washington, D.C. The 1956 lecturer became director of the Royal Aircraft Establishment in 1951 at the age of 36 and was knighted 3 years later. He gained world recognition for his work in connection with the RAE inquiry into causes of the Comet Airliner crashes. The task of nearly complete rebuilding of a wrecked Comet was undertaken and cause of the accidents found under his direction.

LAWRENCE E. YOUNG, a member of the University of Rochester Medical School faculty since 1943 and widely known for his research in diseases of the blood, will succeed WILLIAM S. McCANN [*Science* **125**, 19 (4 Jan. 1957)] as Charles A. Dewey professor of medicine and chairman of the department, effective 1 July 1957. Young also will be physician-in-chief of Strong Memorial Hospital, teaching hospital of the medical school.

LAURENCE McKINLEY GOULD, president of Carleton College and a geologist by profession, has been appointed director of the U.S. Antarctic Program for the International Geophysical Year. Gould, who was a member of the 1928–30 Byrd Antarctic Expedition, will direct the scientific program of geophysical observations during 1957–58 at six stations, including one jointly operated by the U.S. and New Zealand, and will also coordinate the U.S. effort with those of the 11 other nations participating in the Antarctic Program.

EDWARD W. COMINGS, head of the School of Chemical and Metallurgical Engineering, Purdue University, has received the William H. Walker award of the American Institute of Chemical Engineers.

CLARENCE L. SNYDER, electrical engineer who pioneered in the study of storage batteries, has retired from the National Bureau of Standards after 39 years of service. His career at NBS has been devoted primarily to work on battery separators. Snyder also has made significant contributions to the development of nonspillable aircraft batteries.

Snyder graduated from the University of Colorado in 1914 with a degree in electrical engineering. He taught for 3 years at Eastern State Vocational School in Oklahoma before going to Washington in 1917 to start his government career.

GEORGE W. HOOVER, Navy commander, received the space flight award of the American Astronautical Society at its second annual meeting in New York on 7 Dec. The award was presented in recognition of his efforts in the Project Vanguard earth satellite program.

ARTHUR V. TOBOLSKY of Princeton University has received the Bingham medal of the Society of Rheology for his research on the elastoviscous properties of polymeric materials and the kinetics of polymerization reactions.

FRANCIS C. FLINT, technical director of the Hazel-Atlas Glass Division of the Continental Can Company, has been chosen to receive the 1957 Albert Victor Bleininger award of the Pittsburgh Section of the American Ceramic Society. Presentation will be made on 15 Mar. during a dinner at the Penn-Sheraton Hotel, Pittsburgh, Pa.

WILLIAM E. ADAMS, Raymond professor of surgery at the University of Chicago, recently spent several months in Scotland as guest professor of surgery at the University of Glasgow. He also gave addresses at the University of Aberdeen, the Royal College of Surgeons in Edinburgh, the Royal Academy of Medicine in Madrid, and the University of Madrid. In November he was made an honorary professor of surgery at the University of Madrid.

Recent Deaths

SAMUEL H. ANDERSON, Wanamassa, N.J.; 76; retired physicist who served for 24 years at the Fort Monmouth Signal Corps Laboratory; 20 Dec.

FRANK AYDELOTTE, Princeton, N.J.; 76; former director of the Institute for Advanced Study; 17 Dec.

HOWARD M. GIFFT, Ithaca, N.Y.; 48; professor of engineering and newly appointed dean of faculty at Cornell University; 20 Dec.

EDWARD HAMILTON, Morrisville, N.Y.; 48; assistant director of the State University Agricultural and Technical Institute; 20 Dec.

ARTHUR C. MILLARD, Plainfield, N.J.; 57; engineer with the Bell Telephone Laboratories; 18 Dec.

NICHOLAS H. SNYDER, Trenton, N.J.; professor of ceramics at Rutgers University; 18 Dec.

ERWIN VON SCHLICHTEN, Schenectady, N. Y.; 49; assistant professor of psychology at Union College; 20 Dec.

ALBERT E. WHITE, Ann Arbor, Mich.; 82; professor emeritus and former director of the Engineering Research Institute of the University of Michigan; 18 Dec.

Education

■ The New York Medical College–Metropolitan Medical Center has announced the first American Post-Graduate Assembly in Fertility and Sterility, to be held in New York City at the college and affiliated hospitals from 18 to 31 May 1957. Emphasis in the course will be placed on the clinical aspects of human infertility, including recent advances in diagnosis and therapy. A special feature will be sessions devoted to methods and problems in the organization and administration of sterility clinics, services, and teaching programs. The program of the assembly will consist of lectures, demonstrations, round-tables, operative clinics—including culdoscopy and tubal surgery—ward rounds, and specialty-clinic case presentations.

The course will be conducted by the department of obstetrics and gynecology, and is under the supervision of Abner I. Weisman, chief of the section of fertility and sterility. The faculty of the medical college and 18 guest professors from both North and South America will make up the teaching staff.

The course has been primarily designed for those already interested in infertility. It will afford the opportunity for physicians from other parts of the world (particularly Canada and Latin-America) to learn American methods and discuss their specific problems with leaders in the field in the United States. Arrangements have been made for simultaneous translation from English into Spanish for the benefit of the physicians from Latin-America. All schedules, literature, and outlines of the course will be in both languages.

The course has been arranged at the end of May to allow registrants to attend the annual meetings of the American Society for the Study of Sterility, the Endocrine Society, and the American Medical Association, which will be held in New York starting 31 May. Information and applications may be obtained from Dr. Ralph E. Snyder, Dean, New York Medical College, 1249 Fifth Ave., N.Y. 29, N.Y. Registration is limited, and the tuition is $150.

■ The X-Ray Diffraction Data Card File that is published by the American Society for Testing Materials under the editorship of G. W. Brindley of Pennsylvania State University is now being offered to colleges and universities at an 80-percent discount from the list prices. The discount is offered only on the basis that the card file will be used for classroom instruction. A certification to this effect will be necessary for the special discount to apply.

ASTM acts as business agent for the Joint Committee on Chemical Analysis

by Powder Diffraction Methods, which has compiled data for the identification of approximately 5000 crystalline materials by the Hanawalt method. The Joint Committee is sponsored by the American Crystallographic Association, the British Institute of Physics, the National Association of Corrosion Engineers, and ASTM.

The data have been collected from industry, literature, and laboratories and are available on plain 3- by 5-inch cards, 4- by 6-inch Keysort cards, and standard IBM cards. The Keysort cards have the Keysort coding around the border with holes punched but not notch coded. Instructions for coding are supplied with the Keysort cards. Literature and a schedule of prices may be obtained from the X-Ray Department, American Society for Testing Materials, 1916 Race St., Philadelphia 3, Pa.

■ The National Science Teachers Association published the first issue of its new secondary-school publication, *Tomorrow's Scientists,* last October. This 8-page bulletin is designed to bring to the junior- and senior-high-school student recent advances in the scientific fields, science activities for students, career and guidance information, student reports of projects that demonstrate a high level of achievement, science quizzes, and announcements of new science books.

This publication will have six issues during the current school year. The subscription rate is 50 cents per subscription, with a minimum of five copies ($2.50) to any one address. For further information write to the editor, Robert H. Carleton, NSTA, 1201 16th St., Washington 6, D.C.

■ A gift of $300,000 to Dickinson College for its development program has been made by C. Scott Althouse of Reading, Pa., textile researcher and president of the Althouse Chemical Company. The gift is specifically for a new science building that is to cost $600,000. The college will seek to match Althouse's contribution with support from alumni, industry, and other sources. Ground will be broken next June.

Grants, Fellowships, and Awards

■ The U.S. Public Health Service has just announced a grant of $75,000, renewable for 3 years, to promote the training of research scientists at the Jackson Memorial Laboratory, Bar Harbor, Me. The laboratory is well known for its research in the relation of heredity to cancer and other diseases and is recognized as perhaps the major source of standardized animals for medical and biological research.

Recognizing the need for expert investigators in these fields, the laboratory has for years devoted a part of its energies to the training of workers for its own use and for other institutions. These trainees have ranged from youngsters of high-school age to mature and established scientists seeking special training and experience with the laboratory's unique materials and methods. About 70 such "students" from all over the world have participated in the laboratory's program each summer. A lesser number have stayed throughout the year. The USPHS grant will make possible significant improvements in this program.

■ The National Science Foundation has announced that 326 grants totaling $5,963,724 were awarded during the quarter ending 30 Sept. 1956 for the support of basic research in the sciences, for conferences in support of science, for exchange of scientific information, for training of science teachers, and for the support of attendance of scientists at scientific meetings abroad. This is the first group of awards to be made during fiscal year 1957. Since the beginning of the program in 1951, 2821 awards have been made totaling approximately $36 million.

■ The Southern Regional Education Board in Atlanta, Ga., has received a $460,000 grant from the Carnegie Corporation of New York as part of the foundation's national program for research and training in higher education. Carnegie has recently announced this and other grants totaling almost $2 million.

Among the allocations described was a $150,000 grant to the College Entrance Examination Board that will enable the board's commission on mathematics to address itself on a nation-wide scale to the problems of overhauling the mathematics curriculum. The national commission is composed of eminent mathematicians and educators. The results of the commission's work will be made available to the authors and publishers of textbooks, and conferences will be held with secondary school teachers to explain and gain support for the revised curriculum.

This award is part of the foundation's broad program to improve the teaching of mathematics. In 1955 it voted $300,000 to the AAAS for its Science Teaching Improvement Program; then last spring Carnegie gave $277,000 to the University of Illinois for an experimental program for the improvement of mathematics courses in secondary schools.

Still another of the new awards announced is that of $150,000 to the Milbank Memorial Fund for a study of the social and psychological factors in fertility. This work will be undertaken by the Office of Population Research at Princeton University, which will investigate our tremendously increased birth rate and the re-emergence of the large-family pattern in this country.

In the Laboratories

■ Parke, Davis and Company has announced that it has selected a 50-acre site in Ann Arbor, Mich., near the University of Michigan, as the location for its new $10-million Medical Research Center. The new structure is expected to be completed by early 1959, and will supplement the firm's present research facilities. Leon A. Sweet, vice president and director of research, heads the company's 400-member research staff. The number will increase substantially when the new research center is completed.

■ In a move to further expand its activities in the broad field of forest products, the Borden Company's Chemical Division has established a forest products research group for extensive, long-range work. Its immediate objective is the development of resin and polymer products especially adapted to new applications. Borden's will consider requests from industry for specific research and will solicit cooperative work, in addition to pursuing projects designed primarily to increase the company's manufacturing and marketing potential. The new forest products research group will be headed by Dr. George Kitazawa, former research physicist for the Gillette Company.

■ Arthur D. Little, Inc., has expanded its activities into the high-temperature field and is completing a solar furnace for such research. The staff has long been engaged in extreme low temperature research and the production of equipment for work within 8° of the lowest temperature possible; now it will also be working with temperatures of 3500°F.

Peter Glaser is in charge of the development of a solar furnace of a design significantly different from that of existing units. To be completed by the end of this year, it will serve as a model for others to be offered to other research laboratories in 1957.

■ The Argonne National Laboratory, Lemont, Ill., has announced that the H. K. Ferguson Company of Cleveland, Ohio, has been selected as architect-engineer for the design of the Experimental Breeder Reactor II, which has been authorized as part of the Atomic Energy Commission's 5-year program for the development of competitive electric power from nuclear energy. The sodium-cooled EBR-II will be built at the National Reactor Testing Station, and will be designed to produce 62,500 kilowatts of heat and 20,000 kilowatts of electricity.

Reports

Isolation from Human and Pork Lung of an Inhibitor of Virus Hemagglutination

Aqueous extracts of egg white (*1*), blood-cell stromata (*2*), various animal tissues (*3*), and excretory fluids (*4*) are known to inhibit the hemagglutination of chicken red blood cells by influenza, mumps, and Newcastle disease viruses. Certain plant products such as apple pectin (*5*) will also inhibit viral hemagglutination. It is generally considered that the material responsible for inhibitor activity is a mucoprotein (*3, 4, 6*). However, to the best of our knowledge, no information designed to elucidate the detailed chemistry of these inhibitors has been published.

In an attempt to obtain sufficient material for studies that might help to clarify the chemistry of the virus-inhibitor substances, considerable material of a mucopolysaccharide nature and with high inhibitor activity was isolated from both human and pork lung (*7*). Attempts to increase the purity of our materials, however, led to the isolation of a substance that, although it was not mucopolysaccharide in nature, was apparently responsible for the inhibitory activity of our crude material. The substance was found to contain phosphate, but not sulfate. Incubation of this substance with allantoic fluid containing PR8 virus resulted in a loss of activity, together with a liberation of free phosphate. The Salk method (*8*) was used to measure inhibitor activity.

Three pairs of fresh, normal human lungs were cut into small pieces, dipped in Celite, passed through a mechanical grinder, covered with acetone, and stored at −25°C overnight. The acetone was removed by filtration on a Buchner funnel, and the solid residue was extracted with 3-percent ammonia water for ½ hour at 60°C. The inhibitor material was separated by filtration through Celite on a Buchner funnel, and the *p*H of the filtrate was adjusted with acetic acid to approximately 7. The precipitate that formed was removed by centrifugation, redissolved in 200 ml of 3-percent ammonia water, filtered, adjusted to *p*H 7 with acetic acid, and centrifuged. The supernatant fluids containing material soluble at *p*H 7 were combined, and six volumes of absolute ethanol were added. The precipitate was collected by centrifugation. Weight, 52 g; activity, 4 μg inhibited two units of PR8 virus.

The biologically active precipitate was dissolved in distilled water containing a few drops of 10-percent ammonia water (*p*H 7 to 8), and the protein was removed by shaking the solution a number of times with a 1/4 mixture of amyl alcohol and chloroform after the manner of Sevag (*9*). The mixture was centrifuged to break the emulsion, the clear aqueous layer was acidified (*p*H 6 to 7) with acetic acid, and the active material was precipitated by the addition of six volumes of absolute ethanol. The precipitate was washed several times with absolute ethanol and with ether, then dried at room temperature under a high vacuum. Weight, 20 g; activity, 1 μg inhibited two units of PR8 virus.

The dried powder was extracted with 25 ml of formamide and filtered, and the active material was precipitated from the formamide solution by the addition of 200 ml of absolute ethanol and 25 ml of ether. The precipitate was washed with absolute ethanol and with ether. Weight, 2 g; activity, 0.1 μg inhibited two units of virus.

The inhibitor substance was further purified by dissolving it in 50 ml of distilled water acidified with acetic acid (*p*H 6 to 7) and adding a saturated solution of lead acetate drop by drop until precipitation was complete. The precipitate was collected by centrifugation and washed twice with distilled water. Weight, 200 mg.

One gram of this lead salt was stirred with 10 ml of a freshly prepared 3-percent solution of ammonium sulfide, and the mixture was centrifuged and filtered through a fritted glass filter. The excess ammonium sulfide was removed by warming the solution under reduced pressure at 30 to 35°C. Ten milliliters of absolute ethanol were added to the solution, which was then filtered. After the addition of 10 ml of ether, the solution was allowed to stand at 0°C overnight. Additional material could be obtained by recycling the insoluble fractions.

The precipitate was collected by centrifugation, washed with ethanol and ether, dissolved in 10 ml of distilled water, and treated with 10 ml of a saturated solution of calcium hydroxide. The ammonia was removed by cautiously warming at 40°C under reduced pressure. The excess calcium hydroxide was removed by treating the solution with carbon dioxide gas and then filtering. The calcium salt precipitated as an amorphous powder on the addition of five volumes of ethanol. Weight, 600 mg; activity, 0.01 μg inhibited two units of virus. A crystalline product could be obtained by adding absolute ethanol to turbidity and allowing the solution to stand for several days at 4°C. Elemental analyses (*10*) showed: C, 43.34; H, 5.37; N, 12.01; P, 2.37; and Ash (as sulfate) 10.11 percent. Optical rotation; $[\alpha]^{28}_{D}$, −33° (H_2O, *C*, 0.1).

An ammonium salt could be prepared by treating the calcium salt with ammonium carbonate, adding an equal volume of ethanol, filtering, and then adding ether until precipitation occurred.

Both salts gave a positive test with the Molish and anthrone (*11*) reagents, reduced Fehlings solution after but not before hydrolysis, and gave negative xanthoproteic, Millon and ninhydrin tests for amino acids. The biuret test was positive. The test for hexosamine (*12*) was positive after hydrolysis. The substance was stable at *p*H 8 to 9 but readily lost biological activity at *p*H 4 to 6. The ultraviolet absorption spectrum showed a maximum at 260 mμ. The infrared spectrum showed absorption at 3.0, 6.05, and 6.45 μ, which may be considered to indicate the *R*—CO—NH*R′* grouping (*13*). Electrophoretic analysis showed one component at *p*H 8. At *p*H 4, however, after 15 minutes, four components were observed. We consider this to be due to degradation at low *p*H. No inhibition of the infectivity of PR8 virus in the chick embryo could be found.

When pork lung (*14*) was subjected to the afore-mentioned isolation procedure, the material, so far as could be ascertained by a comparison of biological activity, chemical, electrophoretic, and infrared analysis, was the same as that obtained from human lung. The approximate yield, in both cases, was 100 mg from 10 kg of fresh lung.

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* Present address: U.S. Naval Powder Factory, Indian Head, Md.

19 June 1956

Concentration of Visual Purple in a Retinal Rod of Rana pipiens

The density of the photosensitive pigment in the distal segments of the retinal rods and cones determines the effectiveness of radiation incident upon the retina in evoking a visual response. Only the light that is absorbed by the pigment in the visual cells can be effective in initiating a visual stimulus. Since there are significant losses of light in the transparent media of the refractive apparatus and in the neural layers of the retina, it is of importance to know what portion of the light that finally reaches the distal segments will be absorbed. This can be evaluated by a knowledge of the density of the pigment within the distal segments of the retinal rod.

Several methods have been applied to the determination of the density of visual purple in the distal segment of the retinal rod. One procedure has been to determine the maximum amount of pigment that is extractable from a known number of retinas and to estimate how much light this quantity of pigment would absorb if it were dispersed in an area corresponding to the retinal distribution of rods (*1*). A second method is to estimate the total visual pigment in the outer limb by measuring the minimum molecular weight per chromophore and computing the total content by assay of the carotenoid component (*2, 3*). An additional and completely unrelated method is to compare the scotopic luminosity curve and the spectral absorption curve of visual purple as used by Hecht *et al.* (*4*) in order to estimate the absorption by rod segments in the retina.

A more direct method is to assay the extracted visual purple and to reduce the data to the dimensions of a single distal rod segment, as was attempted by Broda *et al.* (*5*) and Denton (*6*). The problem of light absorption in the distal segments has become increasingly important in the consideration of the mechanism of the initiation of visual response.

In the series of estimations reported here (*7*), *Rana pipiens* were used. The animals were adapated to the dark for 24 hours, the eyes were removed and sectioned, retina and pigment layer were removed, and the pigment layer was separated from the retina. The retinas were washed in Ringer's solution and then very gently shaken in it. This served to detach the distal segments of the rods. The rod segments were separated from the remainder of the retinal debris by straining through fine wire mesh and recovered from the Ringer's solution by low-speed centrifugation. The accumulated rods were resuspended in a known volume of Ringer's solution, and the total number of rod segments in the solution was estimated by means of a hemocytometer (Table 1, column 3). The visual purple was extracted in 5 ml of digitonin solution after the suspended rod segments had been collected by centrifugation at high speed. The absorption spectrum of the resulting solution was measured with a Beckman DU spectrophotometer. The density at 500 mμ is given in Table 1, column 4. The residue remaining after the centrifugation of the first digitonin extract was extracted a second time with fresh digitonin, but it did not contain a measurable quantity of visual purple.

The dimensions of the distal segments of the rods were measured by means of an ocular micrometer. Fifty separate measurements gave an average length of 52.1 μ and a diameter of 7.6 μ. From these figures, the cross-sectioned area of a single rod was computed to be 45.36 μ^2.

Since the number of rod segments in each preparation is known, the contribution of a single rod segment to the density of the total visual purple solution can be computed. This is shown in Table 1, column 5.

Assuming that Beer's law is valid over the ranges of concentration encountered, we can estimate the density of the visual purple in a single rod segment by reducing the cross-sectional area of the solution to that of a single rod. Since the density of the solution for a depth of 1 cm is known from direct measurement, this manipulation is in effect equivalent to computing the density of the solution when its cross-sectional area is equal to that of a single rod and when its depth is permitted to increase until the volume is identical with that of the original 5-ml extraction. This procedure yields a concentration factor by which the contribution of a single rod segment to the density is multiplied to yield the density of pigment in a distal segment of the rod. The concentration factor and the computed density of the visual purple in the rod segment are shown in Table 1. The density of pigment in the rod segment is 0.642 at a depth equivalent to the axial length of the rod, 52 μ, and the density per micron along the axis of the rod is 0.012.

This value is higher than that reported by Broda *et al.* (*5*) or that computed by Hubbard (*3*), and it is of the same order of magnitude as that reported by Denton for another species of frog (*6*). Since this method of assay requires the solubilization of the pigment, the unavoidable losses during processing mean that these are minimal values. In addition, if the distal segments of the rod are not removed intact, there must be a portion of the visual pigment which remains in the retinal layers. The density per micron depth of a distal segment of a rod is a more general and useful value and is obtained by using the value of 52.1 μ for the length of the segments analyzed. This value of 0.01233 per micron is also shown in Table 1.

An additional consideration in estimating the maximal absorption by visual purple in a single rod is the degreee of orientation of the anisotropic molecules (*8*). The absorption of unpolarized light by a solution of randomly oriented anisotropic molecules would be lower than that of a rod that consisted of a series of parallel planes of optically oriented

Table 1. Density of visual purple in retinal rods. The concentration factor is 0.1102×10^8; the computed density of the pigment in the rod segment along the axis (density per rod) (factor) is 0.642; and the density per micron along rod axis is 0.012.

Preparation No.	Number of retinas	Total rods	Optical density at 500 mμ for 1-cm depth of solution	Density per single rod in 5-ml solution at 1-cm depth
1	25	4.06×10^6	0.256	0.063×10^{-6}
2	100	18.175×10^6	1.049	0.058×10^{-6}
3	100	26.18×10^6	1.410	0.054×10^{-6}
			Av.	0.0583×10^{-6}

molecules in which the axes of the successive planes were randomly oriented, but would be greater than that of a case in which the optical axes of the planes were all parallel. The latter situation places an upper limit on the absorption by the completely oriented element of 50 percent of the incident light. Until the detailed orientation of the visual purple molecules is known, this question cannot be resolved.

A density of 0.642 in the distal segment of the rod means that approximately 75 percent of the light incident on the rod segment is absorbed if its path is parallel to the axis of the rod segment. However, the retinal rods do not occur on the optical axis but are distributed peripherally. As a result, a beam of light which is less than the diameter of a rod in cross section may follow a path that will intersect several rods despite the curvature of the retina in the optic cup. If the beam falls at such an angle that it traverses the longest diagonal axis of a single rod, the probability of absorption would increase, for the path length through the rod is greater, and a somewhat thicker layer of photosensitive pigment would be traversed. In this case, the absorption would be 80 percent. If the beam intersected a closely packed, parallel bundle of rod segments at an angle of 45°, the absorption would be nearly 90 percent. Therefore, in species possessing a fovea, peripheral vision not only has the advantage of the higher absorption because of higher pigment concentration but also has the increased possibility of light gathering by the obliquity of the incident light.

As shown by Hecht *et al.* (*4*), a single quantum hit in each of only a small number of rods is required to produce a visual sensation in man at threshold. With absorptions by the individual elements of this order of magnitude or even considerably lower in the case of the mammalian eye, as suggested by Hubbard (*3*), the probability is high that the effective photochemical event will occur in the surface region of the receptor cell and that the resulting activated products will be in the optimal position for the initiation of the process that leads to membrane asymmetry and the initiation of an impulse, if indeed it can be assumed at this time that a mechanism as direct as this is involved in the initiation of the impulse.

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29 October 1956

Radiocarbon Age Estimates Obtained by an Improved Liquid Scintillation Technique

The physical and chemical techniques used in our laboratories for radiocarbon dating have already been described (*1*, *2*). The purpose of this work is to indicate an important modification in method and to report on the samples measured to this time (*3*).

In the liquid scintillation method of radiocarbon dating, the sample carbon is introduced into the sensitive volume as the solvent component of the scintillator or as a suitable diluent. Because of the low energy of the C^{14} beta spectrum and the resultant feeble light pulses, it is necessary to use a scintillator with as high a fluorescence efficiency as possible. This is particularly important for a single-channel counter used at ambient temperatures. We therefore first attempted the synthesis of the solvent component of the liquid scintillator from sample carbon (*1*), for this insures maximum luminescence output in the final scintillator solution.

On the other hand, for routine operation, the complexity of the chemical syntheses of such solvents as toluene and xylene suggests the use of an appropriate diluent whose chemical synthesis is less involved, and whose presence in the liquid scintillator does not appreciably reduce the luminescent output. In an earlier report (*2*), we showed that methanol could be used as a diluent in a liquid scintillator for the detection of natural radiocarbon with a 30-percent efficiency. An examination of Fig. 1 in that report shows, however, that labeled carbon concentrations of greater than 0.1 g/ml of scintillator are not feasible, for then the C^{14} spectrum and the photomultiplier noise spectrum overlap too markedly. A specially selected K1190 photomultiplier was used in this work. Subsequently, three of six C467 Dumont tubes tested have been found to give approximately the same low noise level as this selected experimental tube.

Recently (*4*) it has been shown that the use of naphthalene as the second solvent reduces the quenching action of many materials in liquid scintillators. Using this technique, we were able to introduce appreciable quantities of trimethyl borate (*5*) into a liquid scintillator without seriously affecting the efficiency of fluorescence. Since the methyl borate can be prepared quite readily from methanol, the possibility of its use as the labeled component for routine radiocarbon dating has been investigated.

The preparation of methanol from sample carbon was performed by procedures already described (*2*). The conversion of the methanol to methyl borate was accomplished by a modification of a procedure of Schlesinger *et al.* (*6*). In principle, the method involved the esterification of boric oxide with methanol and the separation of the resultant azeotrope. In a typical synthesis, 18.80 g (0.59 mole) of methanol was placed in a 100-ml flask fitted with a semimicro fractionating column, and 13.72 g of finely powdered boric oxide was added in four portions through a side arm. Following the addition of each portion, the contents of the reaction vessel were refluxed gently. Upon completion of the addition, the reaction mixture was refluxed a further 2 to 3 hours. The contents were then distilled through the column, and the methanol-methyl borate azeotrope was collected in a receiver immersed in dry ice. The azeotrope was then separated by rapid addition of 4.2

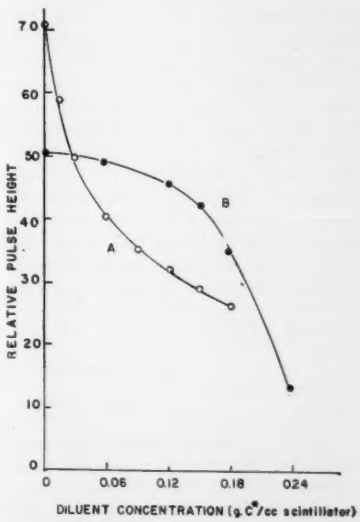

Fig. 1. Dilution curves showing pulse height, relative to anthracene at 100, as a function of diluent concentration expressed as grams of labelled carbon per milliliter of scintillator. *A*, Diluent methanol in solution of 4 g/lit of terphenyl and 0.1 g/lit of 1,4 di-2-(5-phenyloxazolyl)-benzene in xylene; *B*, diluent methyl borate in solution of 3 g/lit of phenylbiphenylyloxadiazole, and 70 g/lit of naphthalene in xylene.

g of dried anhydrous lithium chloride. The flask was vigorously agitated until two liquid layers were formed. The top layer, consisting of almost pure methyl borate, was separated in a micro separatory funnel. Further purification consisted of a distillation through a semimicro fractionating column, followed by a second lithium chloride separation, and finally a further fractional distillation. A boiling range of 67.5 to 68.5°C was observed, and a yield of 71 percent was obtained. The remaining methanol could be recycled for a further synthesis if required.

For comparison, the dilution curve for methyl borate is shown in Fig. 1. It is evident that despite the initially lower luminescence efficiency of the 2-phenyl-5-(4-biphenylyl)-1,3,4-oxadiazole (PBD) (3 g/lit), naphthalene (70 g/lit) scintillator, at C* concentrations greater than 0.03 g/ml this solution is superior to the methanol diluent. For methanol in a 20-ml cell, a net C^{14} counting rate of 7.39 ± 0.08 count/min over a background of 8.18 ± 0.05 count/min was the optimum counting rate obtained for contemporary carbon (*2*). For methyl borate with the same scintillator volume, we have realized a net C^{14} counting rate of 10.07 ± 0.08 count/min over a background of 4.26 ± 0.04 count/min. This improvement represents an extension in the range of the method of roughly 5000 years.

To date, six documented samples have been dated in our laboratories. The documentation was provided by the collector and is briefly summarized in Table 1. One sample (S-4) was dated by the methanol method because of the limited amount of sample available. The others were converted to trimethyl borate before counting. In each case, the unknown sample and the background dummy containing petrochemical carbon were alternated every 24 hours, thus bracketing each sample with two background counts. This procedure was facilitated by the use of two identical cells that had previously been carefully investigated for differences in radioactive content. The age assigned to any sample is the average age as determined by two 24-hour counts. The error assigned to any age is the statistical counting error. The results are summarized in Table 1.

Samples S-3 and S-4 have significance as part of a study by R. Lougeee of postglacial upthrusts on glacial seashores on either side of the Atlantic Ocean. According to N. R. Gadd, samples of wood from sample S-17 have previously been dated $11,050 \pm 400$ years by J. L. Kulp at Lamont Geological Observatory (sample L-190A), older than 30,840 years at Yale University (sample Y-242), and older than 40,000 years at the U.S. Geological Survey (sample W-189).

Samples S-6 and S-7 have been reported as greater than 38,000 years by the U.S. Geological Survey. Our results on samples S-6 and S-7 can be considered to be in good agreement with those obtained by other methods, but N. R. Gadd (*7*) suggests that geologic evidence would indicate that our sample S-17 should be much older than reported, and similar in age to samples S-6 and S-7.

Our experience with the afore-mentioned methods indicates that they are suitable for routine use in radiocarbon age estimates and offer certain attractive advantages in terms of simplicity of operation over other suggested scintillation techniques (*8*).

These methods also have sufficient accuracy to make them attractive in comparison to gas-counting techniques (*9*). The chemical syntheses of methyl borate are relatively simple. The electronic equipment is also of minimum complexity and avoids the use of anticoincidence equipment or refrigeration. However, in common with all other methods, problems of electronic drift and sample contamination may reduce the over-all precision below the statistically quoted limits. Increasing the scintillator volume would be expected to yield a higher precision but would necessitate the use of larger specimens and larger-scale syntheses.

Table 1. University of Manitoba radiocarbon dates.

Description	Sample No.	Age (yr)
Baie St. Catherine, Quebec. Driftwood from 13 to 20 ft below Mic Mac Terrace. Collected by R. Lougee, department of geography, Clark University.	S-4	3150 ± 130
Amherst, Nova Scotia. Stump from drowned forest in Bay of Fundy near Amherst. Collected by R. Lougee.	S-3	5300 ± 150
Missinaibi River, Ontario. Wood from a flat horizon of Missinaibi River area, from mouth of the Soweska River. Collected by O. L. Hughes, Geological Survey of Canada.	S-6	29,000 ± 1500
Missinaibi River, Ontario. Peat from the same area as sample S-6. Collected by O. L. Hughes.	S-7	38,500 ± 3500
St. Pierre-les-Becquets, Ontario. Wood. Collected by N. R. Gadd.	S-17	20,200 ± 800
Edmonton, Alberta. Alberta wood from the upper till of the Edmonton district. Collected by C. P. Gravenor, department of geology, University of Alberta.	S-15	21,600 ± 900

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16 November 1956

Acetylrhodopsin

The photosensitive pigment of rod vision, rhodopsin, is a chromoprotein composed in equimolar parts of the protein opsin and the carotenoid retinene (*1*). During the course of an investigation of some of its chemical properties, a successful attempt was made to acetylate rhodopsin. The acetylated pigment possesses spectral and photosensitive properties essentially identical with those of rhodopsin. Once bleached, however, the modified protein does not regenerate in the presence of the neo-b isomer of retinene as does bleached rhodopsin (*2*). The object of this paper is to describe the preparation and some of the properties of acetylated rhodopsin (*3*).

Cattle rhodopsin was prepared by methods previously described (*4, 5*). It was purified further by passage through columns of mixed-bed, ion-exchange resins, which remove amino acids and peptides in addition to other impurities of low molecular weight (*6*).

The optical properties of rhodopsin provide a useful index of purity. The absorption spectrum in aqueous digitonin solution has maxima at about 498 and 350 mμ, associated with the carotenoid chromophore, and a sharp peak at 278

mμ because of the protein opsin (*7*). A minimum occurs at about 400 mμ. Since most impurities tend to raise the absorption at short wavelengths, the lower the ratios of the optical densities at 278 and 400 mμ to the density at 500 mμ (278/500 and 400/500 ratios), the purer in general is the preparation. In the best preparations, these indices have the following values: 400/500 ratio, 0.22 to 0.26; 278/500 ratio, 2.1.

The optical density at 500 mμ can be used also to determine the concentration of cattle rhodopsin, for its molar extinction is known to be 40,600 (*8*). The concentration of acetylrhodopsin was similarly determined, using, however, the extinction coefficient of rhodopsin. The coincidence of position and shape of the 500 mμ band of the two proteins is taken as sufficient evidence for the equivalence of their coefficients (see Fig. 1).

Rhodopsin was acetylated by the method of Fraenkel-Conrat (*9*). To solutions of rhodopsin in 1-percent digitonin, half-saturated with sodium acetate and chilled to 0°C, acetic anhydride (99 percent pure) was slowly added (3.0 ml/g of protein) during 1 hour. On the average, the rhodopsin solutions contained about 6 mg of protein in a final concentration of about 0.3 percent. After this treatment, the protein was dialyzed for 2 to 5 days at 4°C against large volumes of distilled water, previously adjusted to *p*H 7 with 1*M* sodium hydroxide. This procedure is known to acetylate free amino, sulfhydryl, and phenolic hydroxyl groups of proteins (*9*, *10*).

The free amino groups of rhodopsin before and after acetylation were determined by the ninhydrin method (*11*), using alanine as standard. It should be pointed out that in this procedure the protein is denatured by heat. The percentage acetylation is based therefore on the free amino groups of the denatured and hence bleached protein—that is, denatured opsin—not on those of native rhodopsin.

Acetylation had no significant effect on the absorption spectrum of rhodopsin. Neither the positions of the absorption bands in the spectrum nor their relative optical densities were markedly altered. This is indicated in Table 1. The introduction of acetyl groups on the protein apparently does not disturb significantly the nature of the opsin-retinene relationship; it leaves retinene attached to acetylated opsin in such a way that the characteristic 500 mμ band of the chromophore remains unaltered (Fig. 1).

An average of 13 amino groups per molecule was found in denatured rhodopsin (Table 1). This is a small number for a protein of molecular weight about 40,000 (*1*) and may account in part for its insolubility in the absence of solubilizing agents. About 74 percent of the amino groups were acetylated by our procedure. This is the usual result obtained with this method (*10*, *12*). No attempt has yet been made to prepare partially acetylated rhodopsins.

Although acetylation had no measurable effect on the absorption spectrum of rhodopsin, it abolished the capacity of rhodopsin to regenerate after bleaching. Ordinarily, bleached rhodopsin regenerates readily on the addition of neo-b retinene and incubation in the dark (*2*). The regeneration of acetylated rhodopsin after bleaching was tested immediately after acetylation but before dialysis. The solutions therefore contained about 2.5*M* sodium acetate; for this reason, the comparison solutions of rhodopsin were brought to the same salt concentration. It is known that the regeneration of rhodopsin is optimal at about *p*H 6.5 (*5*); but since this property might have been altered by acetylation, the acetylated preparations were tested over a range of *p*H from 4 to 7.5. In each case, rhodopsin and the acetylated pigment were bleached in orange (nonisomerizing) light, neo-b retinene in digitonin solution was added in excess, and the mixtures were incubated in the dark at 25°C until all changes were complete.

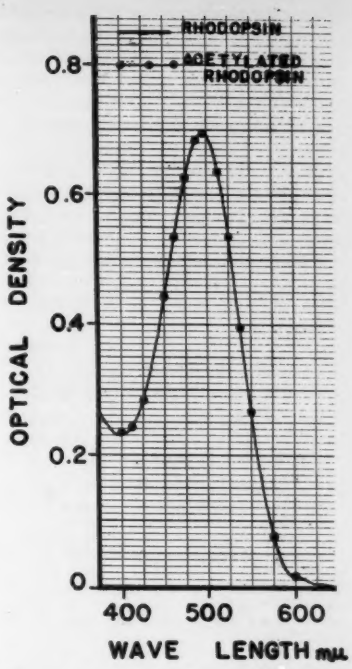

Fig. 1. Absorption spectra of rhodopsin and acetylated rhodopsin (22.5°C, *p*H 6.5).

Table 1. Extent of acetylation of free amino groups in rhodopsin.

Experiment No.	Preparation	Optical density ratio: 400 mμ / 500 mμ	Optical density ratio: 278 mμ / 500 mμ	Free amino groups per mole* (No.)	Acetylation of free amino groups (%)
1	Rhodopsin	0.330	2.83		
1	Acetylrhodopsin	0.290	2.71		
2	Rhodopsin	0.270	2.73		
2	Acetylrhodopsin	0.276	2.59		
3	Rhodopsin	0.273	2.44	14.5	
3	Acetylrhodopsin	0.266	2.38	3.9	73
4	Rhodopsin	0.266	2.55	11.1	
4	Acetylrhodopsin	0.283		2.8	74
5	Rhodopsin	0.245	2.90	11.5	
6	Rhodopsin	0.251	2.71	12.3	

* These determinations involve the denatured and hence bleached pigment, not native rhodopsin or acetylated rhodopsin.

The results of a typical experiment are as follows. At *p*H 6.5, the rhodopsin blank regenerates 83 percent; at *p*H 4.0, 5.0, 6.5, and 7.5, the acetylated rhodopsin regenerates 6.0, 7.0, 5.0, and 5.0 percent, respectively. It is apparent that under conditions in which rhodopsin regenerates 83 percent, acetylated rhodopsin indicates only a trace of regeneration, perhaps to be ascribed to traces of lightly acetylated or unacetylated pigment. Dialysis at 4°C against distilled water to remove the sodium acetate did not alter this relationship, although it did markedly decrease the regeneration of unacetylated rhodopsin.

Acetylated rhodopsin is very much less stable than the unacetylated pigment. When it is stored at 4°C in the dark, almost all the acetylated pigment is bleached within 2 weeks, though a similar rhodopsin solution is stable under the same conditions.

How can one explain that acetylation, though it does not affect the relationship between opsin and its chromophore in rhodopsin, prevents regeneration after bleaching? The native structure of rhodopsin, like that of other proteins, is probably maintained in part by a network of internal hydrogen bonds and also by the attachment of the prosthetic

group, for rhodopsin is much more stable than opsin (*13*). If, as seems likely, acetylation removes numbers of amino groups that formerly had been engaged in hydrogen bonding, this would loosen the structure of the protein, making it more susceptible to denaturation. Presumably, the structure in the neighborhood of the prosthetic group is still intact, as evidenced by the unchanged optical properties. The bleaching process, by dissociating the prosthetic group, removes a further stabilizing influence, and the liberated acetyl opsin readily denatures.

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30 October 1956

Route of Elimination of Anthracene and 9-Methylanthracene Involving Protein Binding

The emphasis of current research on the mechanism of carcinogenesis has been on the binding of the carcinogen or its metabolites with tissue protein. The relationship between binding and carcinogenic potentiality has been studied by changing the chemical agent (for example, carcinogenic, weakly carcinogenic, and noncarcinogenic agents, azo dyes, polynuclear hydrocarbons, an aromatic amine, and an acridine), and the tissue (for example, liver of rat, mouse, guinea pig, rabbit, cotton rat, and chicken; and skin of mouse, hamster, rat, rabbit, and guinea pig).

From their correlations with azo dyes, Miller and Miller proposed a protein- or enzyme-deletion theory of carcinogenesis (*1, 2*). These authors considered not only the maximum value of protein binding but also the rates of increase and decrease of the maximum (*2*). Following the demonstration that the carcinogens 3,4-benzpyrene (*3*) and 1,2,5,6-dibenzanthracene (*4*) were bound to mouse-skin protein, three groups reported on the relationship between skin protein binding of hydrocarbons and the carcinogenic potential of the hydrocarbon-tissue combination. Moodie, Reid, and Wallick concluded that noncarcinogens are either not bound to protein at all or are much more weakly held than are carcinogens (*5*). Woodhouse (*6*) found no relationship between protein binding and carcinogenic potentiality. Heidelberger and Moldenhauer (*7*) found a positive relationship between the maximum value of protein binding and carcinogenic potential in seven out of eight instances.

It was established that the binding of 9,10-dimethyl-1,2-benzanthracene-9,-10-C^{14} with mouse-skin protein was dependent on the dose of carcinogen per unit area of skin and related to the weight response of the treated skin (*8*). This study has now been extended to several hydrocarbons, each of which was applied in a series of graded doses (*9*). A significant difference was observed in the rates of elimination from mouse-skin protein between two trinuclear hydrocarbons and two tetranuclear hydrocarbons. Twenty-four hours after application to mouse skin, the protein binding of anthracene-9,10-C^{14} (a noncarcinogen) and of 9-methylanthracene-9,10-C^{14} (a noncarcinogen) (Tables 1 and 2) was shown to be much lower than the protein binding of 9,10-dimethyl-1,2-benzanthracene-9,10-C^{14} (*8*) (a potent carcinogen) and of 1,2-benzanthracene-9,10-C^{14} (*10*) (a weak carcinogen, *11*).

The relatively rapid elimination of anthracene-9,10-C^{14} and of 9-methylanthracene-9,10-C^{14} might have taken place through a transient protein-bound phase or might not have involved any appreciable protein binding. The previous observations (*8, 10*) with the series of graded doses showed binding to be dose-dependent and hence suggested that measurements made within 24 hours after the application of the highest dose would be necessary to detect a transient protein-bound phase.

The experimental procedure has been described (*8*). The data (Tables 1 and 2) demonstrate that the relatively rapid elimination of anthracene-9,10-C^{14} and 9-methylanthracene-9,10-C^{14} from mouse skin involve a transient protein-bound phase of at least the same order of magnitude as that observed with 9,10-dimethyl-1,2-benzanthracene-9,10-C^{14}. Thus, the maximum value of protein binding is independent of the carcinogenic activity and structure of the hydrocarbon. Data were obtained by feeding rats the five azo dyes 3′-methyl-4-dimethylaminoazobenzene, 4-dimethylaminoazobenzene, 4′methyl-4-dimethylaminoazobenzene, 3-methyl-4-monomethylaminoazobenzene, and 2-methyl-4-dimethylaminoazobenzene. The last three dyes were of low carcinogenic potentiality, and two of these three experiments did not support a positive relationship between carcinogenicity and extent of binding with liver protein (*2*). The results with the polynuclear hydrocarbons differ from the azo dye data (*2*); no positive relationship was established between the rate at which the maximum of protein binding was attained and carcinogenic potential. Also in contrast with the azo dyes—specifically the very weakly carcinogenic dyes 2-methyl-4-dimethylaminoazobenzene and 3-methyl-4-monomethylaminoazobenzene (*2*)—the protein binding of anthracene and of 9-methylanthracene receded faster from their observed maxima than the protein binding of 9,-10-dimethyl-1,2-benzanthracene and 1,-2-benzanthracene.

Thus there is no experimental demon-

Table 1. Incorporation of radioactivity by mouse skin following the application of anthracene-9,10-C^{14} (0.208-percent series). Each determination was made on the pooled tissues of four mice. Each dose, 104 μg (1860×10^3 count/min) was applied over 3.46 cm^2 of skin. The analyzed dose was 76.3 μg (1365×10^3 count/min) of hydrocarbon over 2.54 cm^2 of skin. Each result is the average of two determinations.

Time after application (hr)	Total activity of whole homogenate (count/min)	Specific activity (count/min mg)	
		Particulate protein	Supernatant protein
0.5	414,000	543	1150
17	62,800	205	667
24	42,100	76	157

Table 2. Incorporation of radioactivity by mouse skin following the application of 9-methylanthracene-9,10-C^{14} (0.225-percent series). Each determination was made on the pooled tissues of four mice. Each dose, 113 μg (1860×10^3 count/min) was applied over 3.46 cm^2 of skin. The analyzed dose was 83.7 μg (1365×10^3 count/min) of hydrocarbon over 2.54 cm^2 of skin. Each result is the average of two determinations.

Time after application (hr)	Total activity of whole homogenate (count/min)	Specific activity (count/min mg)	
		Particulate protein	Supernatant protein
0.5	1,490,000	1410	1600
17	31,400	35	50
24	18,400	30	*

* One determination yielded 43 count/min mg; the other was too low to measure.

stration of a relationship between gross protein binding of hydrocarbons and a metabolic route that is specific to the carcinogenic process (*12*). In this study of contact carcinogenesis, there has been no identification of a specific metabolic route distinguishable from detoxication. The degradation of a hydrocarbon applied to the skin should involve enzymes, in view of which the results are reasonable. It is of interest that two examples of high metabolic activity in the skin have been found.

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9 July 1956

Sex Difference in Eosinophil Counts in Tail Blood of Mature B_1 Mice

Eosinophil counts in tail blood of mice vary with the phase of the daily adrenal cycle (*1–4*) in males (*1, 4, 5*) and in females (*6*) of several inbred strains and their hybrids. Strain differences in characteristic eosinophil levels—obtained at the daily time of high counts—have also been described (*7*). The study reported here (*8*) led to the additional detection of sex differences in the eosinophil count of mature mice of an inbred strain.

The mice studied were of a subline of the C_{57}-black stock (B_1) which had been maintained in the Division of Cancer Biology at the University of Minnesota by brother-to-sister mating for more than 20 generations. The animals were 8¼ months ± 1 week of age at the time of study. For 7 days prior to the study, they were singly housed in a room maintained at 25.6 ± 0.6°C and illuminated from 6 A.M. to 6 P.M. and darkened from 6 P.M. to 6 A.M. Purina Fox Chow and tap water were available to the mice from the time of weaning and throughout the study. Except for the activities associated with cleaning the cages, feeding the mice, and filling the water bottles, the animals were not intentionally disturbed from birth until the time of study. The study was begun at 8:30 A.M. and ended at 8:30 A.M. the following day. It involved eosinophil counts on tail blood obtained from separate groups of mice at 4-hour intervals. Each mouse was thus used for venesection only once. The assembly-line procedures employed for eosinophil counts have been described (*7*).

Figure 1 shows the mean count ± 1 standard error for the two sexes. The 24-hour eosinophil rhythm stands out clearly for each sex, in agreement with the results of earlier work on this subject. But the level around which the mean count cycles in the two sexes, which was previously not compared, is not the same in the two sexes as far as the stock and age-group studied are concerned (Fig. 1). The females exhibit lower counts than the males, without any overlap of mean counts throughout the 24-hour period. Subsequent work on the same mice revealed that the mean paired adrenal weights of the females were higher than those of the males and that the ascorbic acid concentrations in glands from females were higher than in glands from males.

The observation of a sex difference in adrenal weight of B_1 mice extends to this stock observations on the sexual dimorphism of the adrenals, which was reported earlier for several animal forms (*9*). The sex difference in eosinophil count deserves more study, for it may be related to sex differences in adrenal secretory behavior, as anticipated but not yet reliably established (*9*).

The possible relation of the sex difference in eosinophil level to a sex difference in adrenal secretory activity comes to mind in view of the known eosinopenic effect of both cortical and medullary adrenal hormones (*2*). The role played by interaction of the longer estrus cycle (*10*) with the daily adrenal cycle (*2, 4, 6*) which maintains the eosinophil rhythm must also be considered. But whatever may underlie the differences noted, it seems fair to conclude that, in B_1 mice of the age group studied, eosinophil counts can be shown to be a function not only of strain and of phase of daily cycle but also of sex.

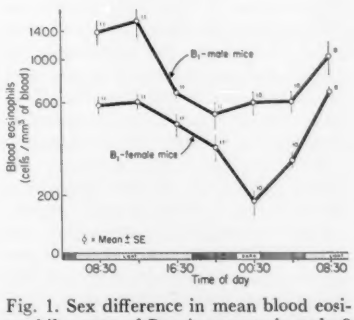

Fig. 1. Sex difference in mean blood eosinophil counts of B_1 mice approximately 8 months old. The number of mice used given above each point; serially independent sampling.

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29 October 1956

Tentative Correlation of Alaskan Glacial Sequences, 1956

A tentative correlation of the Cook Inlet and other Alaskan glacial sequences was published in 1953 (*1*). Since then, additional field and radiocarbon data have accumulated that necessitate some revisions in the 1953 correlation chart. These revisions (Fig. 1) include additions to earlier published glacial sequences and changes in correlation with the type Pleistocene chronology.

Correlations with the standard North American Pleistocene chronology have been revised in accordance with new radiocarbon data relating to both the Mid-continent and Alaskan sequences. Reruns of radiocarbon samples W-76, W-77 (*2*), and also W-174 (*3*) by the more accurate gas-counting method (these samples were originally analyzed by the solid-carbon counting method) indicate that the lower boundary of the

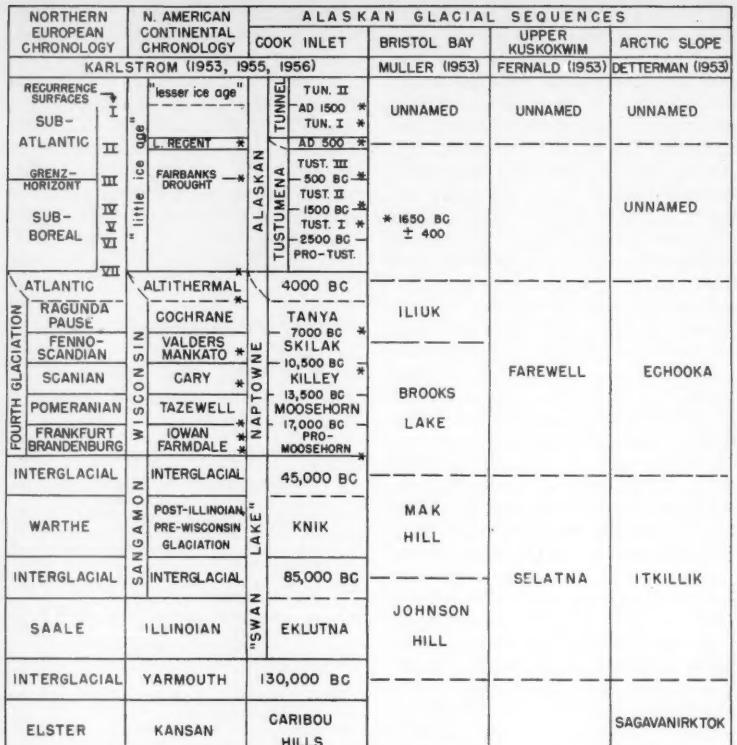

Fig. 1. Tentative correlation of glacial events in Alaska. The stratigraphic boundaries that have been dated by radiocarbon methods are indicated by an asterisk.

Naptowne glaciation of the Cook Inlet region is dated at greater than 36,000 B.C., instead of around 12,000 B.C. as previously published (*4*). These results, combined with the numerous other radiocarbon dates available from the Cook Inlet region, provide a chronology that is in general agreement with the radiocarbon dating of the type Wisconsin sequence (*5*) and with published historical, varve, and radiocarbon dating of the northern European Fourth Glacial (*6*) and postglacial climatic events (*7*). Thus it is evident that the Naptowne and correlative Alaskan glaciations represent all, not part, of Wisconsin time, as previously considered, and that the pre-Naptowne and correlative glaciations are of pre-Wisconsin age.

These correlations satisfy parallel sequence and support the concept of essentially contemporaneous past climatic changes throughout the Northern Hemisphere. The radiocarbon-dated glacial chronology strongly implies astronomic climatic controls with glacial events of stage rank being determined by the "Obliquity Cycle" with a periodicity of about 41,000 years, as recently recalculated from celestial mechanics by van Woerkom (*8*). A similar conclusion concerning climatic control of glacial stage events was reached by Emiliani (*9*) from independent studies of deep-sea cores and paleotemperatures of ocean water. Glacial events of substage and lesser ranks with periodicities of between 3000 and 4000 (about 3400), 1000 and 1200 (about 1100), and 500 and 600 (about 550) years may be genetically related to the tide-generating force curve (*10*), which was also calculated from celestial mechanics. The dates applied to glacial stage events beyond the range of the radiocarbon method in the Cook Inlet chronology are estimates based on a correlation of the glacial sequence with the Obliquity Cycle curve.

The subdivisions of the chronology shown in Fig. 1 are placed near culminations of interglacial, interstadial, and retreatal phases of lesser rank which preceded significant periods of general glacial advance. By definition, then, each recognized subdivision encompasses both an interval of general glacial advance and the following interval of general glacial retreat. This convention, it is believed, emphasizes the natural divisional boundaries that are most directly recorded by geomorphic and stratigraphic evidence in glaciated regions, provides a convenient method of systematic subdivision of glacial periods into their subordinate components, and cuts the nomenclature problem in half by eliminating the necessity of naming both the advancing and retreating phases of each glacial fluctuation.

The correlation of the Alaskan glacial sequences shown in Fig. 1 has been done in direct consultation with E. H. Muller (*11*), A. T. Fernald (*12*), and R. L. Detterman (*13*) of the U.S. Geological Survey. Precise correlation of morainal sequences of differing complexities from widely separate regions of dissimilar topographic and climatic character is difficult in the absence of critical fossil or radiocarbon data. The correlation problem is further complicated by the recent recognition of a post-Illinoian, pre-Wisconsin glaciation in the Mid-continent region (*14*). Although this glaciation has yet to be formally established in the type North American section, geologic data in Alaskan regions where detailed information is available support consideration of this glaciation as an important climatic event of stage rank during Sangamon time. Numerous correlation problems remain, and the accompanying chart should be taken as a somewhat improved but still preliminary correlation that is subject to refinements as additional critical field and radiocarbon data are obtained.

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14. R. F. Flint and M. Rubin, *Science* 121, 649 (1955); R. F. Flint, *Am. J. Sci.* 254, 265 (1956); M. Rubin, "Radiocarbon chronology of glacial events during Wisconsin time," Ph.D. thesis, Univ. of Chicago (1956).

12 October 1956

Book Reviews

A Study of Thinking. Jerome S. Bruner, Jacqueline J. Goodnow and George A. Austin. Wiley, New York; Chapman & Hall, London, 1956. 330 pp. Illus. $5.50.

One of man's most impressive and important characteristics is his ability to group discriminably different events into meaningful and useful categories. For example, although there are an estimated 7 million or more discriminable colors, we get along with only a few color names. Or, with little information, people will classify others as intelligent or not, friendly or not, and so on. Now, although it is clear that such groupings are made and are efficient, we have known relatively little of the way in which intelligent adults arrive at classifications of new events when these events might be categorized in a number of different ways.

In their attempt to provide an answer to this question, the authors of *A Study of Thinking* have written an exciting and thought-provoking book. It can be recommended to persons outside, as well as within, the field of psychology because of its lively and clear prose, and because the authors have constantly related their findings to parallels in everyday life. Finally, the book is of interest because of the proposed solution to the aforementioned problem, one that will surely arouse controversy in the field of psychology.

The book is divided into three parts. The first presents a discussion of the nature of categories and the problems men encounter when using them. The second part presents and analyzes experimental results from an extensive research program. The third, an appendix, is a worthwhile discussion of language and categories by Roger W. Brown.

It is in the second part of the book that the authors' thesis is presented. They argue that, in attempting to place a new event in some category, men approximate ideal, abstractly describable, rational "strategies," and that the strategy approximated will vary as the experimental conditions change. Furthermore, these strategies are conceived of as major determiners of individual choices within a sequence of choices. An example of initial responses in two different strategies may be given by a man suddenly dependent for his existence on eating mushrooms but with knowledge of the appearance of only one nontoxic type. If he could find none of his safe type, he might with little risk test one slightly different and increase his supply by only a few mushrooms. Or he might test one differing in several ways from the safe one and at greater risk increase his potential supply much more. Do experimental subjects who make such initially different responses make further choices consistent with two different strategies? The range of facts that is incorporated by this assumption is impressive. However, the relationship between the responses and the inferred strategy is sometimes rather indirect.

Very likely, psychologists who resonate to this type of interpretation will attempt to specify more closely the nature of these strategies. Others who prefer to think in terms of simpler processes may attempt to formulate these problems in different ways. Regardless of the ultimate fate of these organizing concepts, this work will stand as a major contribution to the psychology of thinking.

DONALD A. RILEY
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S. P. Botkin and the Neurogenic Theory of Medicine. L. R. Borodulin. State Publishing House of Medical Literature, Moscow, U.S.S.R., ed. 2, 1953. 184 pp. (In Russian)

Sergei Petrovich Botkin, a teacher of the physiologist I. P. Pavlov, played a catalyzing role in Russian medicine similar to the one played by William Osler in American and English medical practice and education. These two great clinicians were almost contemporaries. Botkin was 17 years old when Osler was born in 1849. He died at the age of 57, the year Osler moved his activities from the University of Pennsylvania to Johns Hopkins University. Both were in many ways alike in their keen intellects, their scientific attitudes to medical theory and practice, their abilities to arouse and sustain the enthusiasm of their many students in the investigation and practice of scientific medicine, and their breadth of interests which far exceeded the boundaries of medicine. Both were well versed in the physical and chemical sciences of their time as well as in philosophy, literature, and sociology. Both looked upon medicine as one important way of serving mankind and both exhibited continued interest in any activities and developments that would emancipate mankind from the unhappy triumvirate of disease, ignorance, and poverty.

The one major difference between these two men was that, while Osler was primarily a great clinician, Botkin was a clinician as well as an experimental physiologist. He was equally at home in the clinic and in the experimental laboratory. The environments in which these two men worked were also markedly different. Osler worked in an industrialized society in an atmosphere of liberalism and progressive thought that characterized life in the United States of America. Botkin, on the other hand, had to carry on his activities in an essentially feudalistic society governed by an unenlightened absolute monarchy with its secret police and its omnipresent censor.

In spite of this environmental difference, the two men shared many views in common. Among other things, these included their appreciation of the importance of psychologic factors in health and disease and the conviction that sound medical practice should not be limited to pharmacotherapeutics.

It appears that Botkin and Osler represented the most rational expressions of the general revolt against polypharmacy and so-called "heroic" medicine in which, to paraphrase Osler, "large quantities of drugs, the actions of which we knew little, were poured into bodies, the actions of which we knew even less."

The emotional expression of this revolt was represented by Hahnemann's homeopathy and his advocacy of the use of highly diluted drugs, and A. T. Still's osteopathy and his proscription of the use of any drugs and his reliance on joint manipulation as the only correct and useful form of therapy.

Osler and Botkin, on the other hand, attempted to apply the principles of scientific analysis and of the available scientific facts to the development of more rational and effective forms of therapy based on careful diagnosis and facts derived from physiology and pharmacology.

The author of this book on Botkin attempts to describe the development of Botkin's therapeutic concepts on a background of the medical thinking and practice then current in Russian, German, and French medical circles. The chief theme of this book may be indicated as follows: (i) The accumulation of scientific knowledge by the second half of the 19th century exposed the inadequacy of

the theory of medicine based on Cullen's ideas of humors as the seat of disease. (ii) This was replaced by the "anatomic" or "localistic" theory of medicine developed by Virchow in Germany and by the "physiologic" or "neurogenic" theory developed chiefly by the Russian clinician Botkin and the Russian physiologist Sechenov. (iii) This neurogenic theory is a specific characteristic of Russian medical thought that originated among a number of Russian physicians even before Botkin, who gave it a more definite expression. I. P. Pavlov and his students developed these concepts into a system of medicine referred to as "nervism." Briefly, the principle of nervism emphasizes the importance of the cerebral cortex in the regulation of physiologic homeostasis, the concept of the organism as a whole, and the importance of environmental factors (including particularly psychologic ones) in health and disease.

According to Borodulin, this neurogenic theory of medicine differed from both the philosophy of vitalism and the mechanistic concepts in biology. Botkin and his followers postulated that, while all living processes, including the psychic manifestations, can be ultimately analyzed in terms of natural laws, they cannot be explained solely on the basis of the known laws of physics and chemistry. The properties of the biological unit (whether it be a single free-living cell or a higher metazoan) cannot be predicted from the properties of the component elements of the organism; no more than the properties of H_2O or of H_2O_2 can be explained on the basis of the characteristics of hydrogen and oxygen. This latter fact does not induce the chemist to resort to mysticism in explaining the properties of H_2O or of H_2O_2 or of a tobacco mosaic virus molecule. By the same token, the biologist does not have to invoke mystical vitalism in order to explain biological phenomena, including those associated with the activity of the cerebral cortex.

Those who attempted to apply mechanically the laws of physics and chemistry to biological systems often ended up by invoking vitalism in relation to the entire organism, because these physicochemical laws cannot explain biological integration. For example, Claude Bernard, an outstanding and careful experimenter who applied physicochemical principles in analyzing various isolated biologic processes, nevertheless resorted to the assumption of some vital "directive force" in the development of an organism from an egg. "The vital force and life," declared Bernard, "belong to the metaphysical world." Botkin and his school of thought escaped that pitfall by developing the idea of the existence of different levels of organization of matter in nature, each level of integration possessing qualities of its own. The quality of life appears at a certain level of organization of particular kinds of matter.

Within the living organism there are various levels of such integration, beginning with integration within each individual cell and leading up to integration of organs and organ systems. The multicellular organism as a whole is integrated by the central nervous system, the cerebral cortex assuming a more dominant role in the higher animals, particularly in man. This dominant role is maintained in relation to somatic, as well as visceral, functions and in the synthesis of these functions so as to adapt the organism to its environment. With the increasing role of the cerebral cortex in the regulation of physiological homeostasis in higher animals, especially in man, there developed greater possibilities for impingement of psychologic factors on various visceral and somatic functions. Thus, the Botkin-Sechenov-Pavlov neurogenic theory of medicine led to the emphasis of the importance of psychologic factors in health and disease.

This philosophy reflected itself in Botkin's therapeutic principles. Thus, he looked upon fever as a defense mechanism (in which the central nervous system played an important role) and did not encourage the excessive use of drugs in combating fevers, a practice that was fashionable among medical circles at that time. He advocated the use of drugs with care and only when they were definitely indicated. Botkin suggested the need for studying the mechanisms used by the organism in combating disease: "It is in this studying of the natural abortive forms [of disease], the learning of the methods used by the organism in combating infection, it appears to me, that we shall find that path that will lead us to the discovery of recuperating, disease-combating remedies." Botkin urged that treatment be directed toward the patient and not just toward a localized disease.

The early physiological orientation of Russian medicine is also indicated by the following curious facts. Although Russian medical science and education, like science and education in general, barely scratched the surface of Russian society during the 19th century (as compared with the Western world), nevertheless the first Russian chair in physiology, as distinct from anatomy, was created in 1860 and was occupied by Sechenov at the St. Petersburg Medico-Surgical Academy 14 years before the first professorship of physiology was established at the University College at London in 1874 and 16 years before it was created in the U.S.A. at Harvard University in 1876.

Twelve years before Russell H. Chittenden at Yale University Sheffield School of Science organized the first course in physiological chemistry in the United States, Alexander P. Borodin was appointed to the chair of physiologic and organic chemistry in 1862 at the same medical academy in which Botkin taught. It is interesting to note that, in addition to his teaching at the Medical Academy and at the St. Petersburg Medical School for women, Borodin published more than 20 papers in physiological and organic chemistry and was the author of about the same number of major musical compositions, including the famous opera *Prince Igor*. In fact, in the Western world Borodin is known almost entirely as a great Russian composer and one of the originators of the national trend in musical composition based on the utilization of Russian folklore.

The direction of Pavlov's research on the psychic aspects of gastrointestinal physiology and later on conditioned reflexes can be traced directly to the influence of the ideas of Botkin. A number of Botkin's other students continued to develop these therapeutic principles in their clinical teaching and practice. One of these students, V. A. Manassein, developed a keen insight into psychosomatic factors in disease. He insisted that psychologic factors not only can produce temporary disturbances in various visceral functions but may also lead to a host of chronic diseases.

Manassein's remarks regarding hospital environments [*The Importance of Psychologic Influences* (St. Petersburg, 1877), pp. 141–48] could be read with profit by many hospital administrators today. "In this respect most hospitals and clinics present a very unhappy picture with their unfriendly uniform wards and their dull monotonous daily routines. Such shameful conditions in our hospitals, in my opinion, are no less harmful to the patients than all the other errors in regard to hygienic and dietetic arrangements, thanks to which many patients perish, not because of their diseases, but because of their hospitals." In such hospital environments "the thoughts of patients have nothing to concentrate on . . . they are therefore invariably centered around their own pains. . . . The first concern of a physician who understands the significance of psychic influences should be with the need for a more cozy appearance of the wards. In this respect, flower arrangements, birds in cages, wall pictures, aquaria, and so forth, would help us, without interfering with hygienic requirements of cleanliness and simplicity, to a large extent to remove that uniform dishearteningly deadly character which reflects itself at present from almost every hospital, from its bare walls, the monotonous uniforms and rows of beds. . . ."

Manassein advocated the utilization of

music in hospitals as well as occupational therapy and various forms of exercise and sports events: "Every well-organized hospital should have various devices for the occupation and amusement of patients, for example, newspapers, books, chess, cards, lotto, billiards." He urged the institution of a program of clinical and basic research on psychosomatic factors in therapy.

Another student of Botkin, V. P. Obraztsov (1849–1920) called attention to the close relationship between the disturbances of visceral and somatic functions, problems of referred pain, the neurasthenic heart, and the role of autosuggestion in cardiovascular disease.

This book represents an important contribution to the history of Russian medical practice and philosophy. It contains a great deal of material entirely unfamiliar to medical scientists in the Western world.

The book also demonstrates the lack of communication and of cross-fertilization of ideas between Russian and Western (particularly English-American) medical and biological laboratories and clinics and the resultant mutual ignorance and lack of appreciation of each other's achievements. Osler knew not of Botkin, nor Botkin of Osler; both would undoubtedly have profited from acquaintance with each other's ideas.

This lack of mutual understanding still persists and is evident in the over-all approach of Borodulin. In discussing the development by Pavlov, Bykov, Speranskii, and others of the Botkin-Sechenov concepts of cortical integration and of the living organism as a homeostatic unit, he seems to be unaware of the important contributions in this field by British and American physiologists. For example, the appearance of Sherrington's *The Integrative Action of the Nervous System* in 1906 is not mentioned. Nor is there any indication of familiarity with Fulton and Keller's demonstration of the principle of encephalization in their elegant publication *The Sign of Babinski—a Study of the Evolution of Cortical Dominance in Primates,* or with Fulton's extensive lobotomy studies in relation to behavioral problems in primates.

Studies related to the organism as a unit have occupied the center of attention of a number of investigators for many years and in many lands. Jacques Loeb analyzed some of these problems brilliantly in *The Comparative Physiology of the Brain and Comparative Psychology* (1902) and in his book *The Organism as a Whole* (1916). J. B. S. Haldane wrote in 1922: "The only way of real advance in biology lies in taking as our starting point, not the separated parts of an organism and its environment, but the whole organism in its actual relation to environment, and defining the parts and activities in this whole in terms implying their existing relationships to the other parts and activities."

The effects of emotions on body processes have been the subject of investigation and discussion by many scientists, from William Beaumont's *Experiments and Observations on the Gastric Juice and the Physiology of Digestion* (1833) to A. J. Carlson's *The Control of Hunger in Health and Disease* (1916), W. B. Cannon's *Bodily Changes in Pain, Hunger, Fear and Rage* (1920), and the excellent current studies conducted by Stewart Wolf and Harold Wolff and Hans Selye's extensive investigations on stress. As a matter of fact, observations on psychosomatic effects go back to antiquity. Maimonides, the famous Hebrew physician-philosopher of the 12th century, emphasized the importance of emotions in health and disease (letter to the Sultan Saladin). The appreciation and further development of scientific principles can best be achieved by maintaining a broad historical and geographic perspective.

This lack of communication is not, however, one-sided. British and American physiologists failed to appreciate and benefit from the contributions of Russian physiologists. As is pointed out so succinctly by Fulton in his *Frontal Lobotomy and Affective Behavior*: "Although the Russian School had a clear awareness of the importance of cortical representation of many visceral functions, neurologists and neurophysiologists in general were extraordinarily slow to appreciate the broad significance of these earlier disclosures."

The elucidation of the role of psychologic factors in the development of disease and the development of an integrative approach to medical research and practice could best be achieved not by periodic mutual "sniping" but by consistent attempts at closer communication and a development of mutual appreciation between Russian and Western medical scientists and practitioners.

SAMUEL A. CORSON
University of Arkansas School of Medicine

Cours de Physique Générale. Electricité. A l'usage de l'enseignement superieur scientifique et technique. G. Goudet. Masson, Paris, ed. 6, 1956. 899 pp. Illus. Cloth, F. 5100; paper, F. 4500.

This large and well-appointed book is one of a series of advanced textbooks in general physics for university students. In addition to the material usually found in American textbooks for graduate students, it contains a considerable amount of descriptive material dealing with electric measurements, instruments, and machinery written in a more elementary style. Beginning with a brief introductory section on vector calculus and the mathematical treatment of periodic functions, it leads the reader through the classical theory of electrostatics, direct currents, magnetostatics, and quasi-stationary electromagnetic phenomena to the general formulation of Maxwell's equations and the theory of electromagnetic waves. In a final section, the author discusses the properties of charged particles, x-rays, atomic and molecular structure, elementary quantum mechanics, electric and magnetic properties of solids, and electron tubes and semiconducting devices.

The classical electromagnetic theory is developed in the conventional manner. The theorems are precisely enunciated, and the derivations are detailed enough to permit independent study. Many representative problems are carried to a complete solution, and Maxwell's equations are illustrated by many applications. On the other hand and in accordance with European practice, student exercises are not included. The mks system of units is used throughout.

Although the book does not seem to present new approaches to the study of its field, it is clear, comprehensive, and up to date. The typographic arrangement is excellent and makes it easy to follow the derivations.

I. ESTERMANN
Office of Naval Research

Parasites and Parasitism. Thomas W. M. Cameron. Methuen, London; Wiley, New York, 1956. 322 pp. $6.75.

This book departs from the point of view and emphasis found in most present-day textbooks of parasitology. It widens the concept of parasitism to include, in addition to parasitic animals, bacteria, fungi, spirochetes, viruses, and rickettsiae and includes among the animal parasites the parasitic annelids, crustaceans, mollusks, and vertebrates not usually included in parasitological textbooks. Moreover, *parasitism* is used in the wider sense of including the whole gamut of relationships from extreme pathogenicity to symbiosis. Parasitism is viewed as a biological phenomenon with examples chosen from fields widely separated systematically. Thus there is little emphasis upon the medical and veterinary aspects of parasitism, except by virtue of the fact that the parasites involved in producing disease in man and animals are often better known than the forms of little or no economic importance.

Although the discussion of parasitism

passes from one systematic group of parasitic forms to another, it is evident that the attempt has been made to utilize these systematic groups mainly to illustrate the complex phenomena of parasitism. The final fourth of the book is devoted to discussion of the principles, so far as they are known, of parasitism, infectious disease, distribution of parasites, control, and host specificity and evolution of parasites. Also included are an annotated bibliography, a classification of parasites, and a glossary and index.

This attempt to shift away from the vertical, systematic treatment of the subject to the more horizontal, functional approach represents a refreshing initial step in the much-needed change of emphasis from presentations of a bewildering array of seemingly unrelated complexity of relationships to a searching for the relating principles in these relationships.

CLAY G. HUFF
Naval Medical Research Institute

Geology and Ourselves. F. H. Edmunds. Philosophical Library, New York, 1956. 256 pp. Illus. $10.

F. H. Edmunds, long a member of the Geological Survey of Great Britain, writes clearly and simply on geology for the nonscientific layman in a style stripped of the usual geologic jargon. The first half of the book is given to a discussion of the elements of geology and its various fields of specialization, while the remainder discusses the significance of geologic factors in the world around us. The book is well done, but its distribution in the United States may be adversely affected by the fact that it draws almost exclusively on illustrations from the British Isles and because the book is rather expensive considering its purpose.

ROBERT C. STEPHENSON
American Geological Institute

Educating Spastic Children. The education and guidance of the cerebral palsied. F. Eleanor Schonell. Philosophical Library, New York, 1956. 242 pp. Illus. $6.

This book, which is divided into four parts, treats of the educational problems and evaluation of the educational difficulties arising from cerebral palsy.

The first part gives a general definition and classification of the various types and causes. A history of the growing interest in the condition follows and describes the progress, especially in America, Australia, and Great Britain.

Part two is concerned with the various surveys especially related to the Birmingham research project. The use of various intelligence scales as measures of intelligence specifically in the cerebral palsied is described, and estimates of intelligence as carried out by many surveys in the different countries are compared.

Part three deals with practical planning for educational facilities for these children and actual and suggested curriculums. Part four deals with psychological and social development, taking into consideration the limitations imposed on the child by his handicap.

This book is a valuable and well-written source of much needed information by teachers and all others dealing with the psychosocial development of the cerebral palsied child. It should stimulate far better understanding and facilities for education of cerebral palsied children.

The only criticism that can be made of this book, in my opinion, is with regard to the title. The term *cerebral palsy* has practically superseded *spastic paralysis* when used for the whole group in America, and such change is occurring more and more in Great Britain. The author mentions in her preface that she is using the term to include the whole group, but the confusion which has arisen from using this term, except specifically for spastics, is the reason that *cerebral palsy* is being more widely used now.

WINTHROP M. PHELPS
Baltimore, Maryland

New Books

Advances in Carbohydrate Chemistry. vol. 11. Melville L. Wolfram, Ed. Academic Press, New York, 1956. 465 pp. $11.

Metallurgical Analysis by Means of the Spekker Photoelectric Absorptiometer. F. W. Haywood and A. A. R. Wood. Hilger & Watts, London, ed. 2, 1956 (order from Jarrell-Ash Co., 26 Farwell St., Newtonville 60, Mass.). 292 pp. $8.50.

Cold Spring Harbor Symposia on Quantitative Biology. vol. XX, *Population Genetics: The Nature and Causes of Genetic Variability in Populations.* Biological Laboratory, Cold Spring Harbor, N.Y., 1955. 346 pp. $8.

Unit Operations of Chemical Engineering. Warren L. McCabe and Julian C. Smith. McGraw-Hill, New York, 1956. 945 pp. $10.50.

Advances in Electronics and Electron Physics. vol. VIII. L. Marton, Ed. Academic Press, New York, 1956. 562 pp. $13.

Hi-Fi from Microphone to Ear. Modern sound-recording and reproduction technique. G. Slot. Philips Technical Library, Eindhoven, Netherlands, 1956. 169 pp.

Ancestors and Immigrants. A changing New England tradition. Barbara M. Solomon. Harvard University Press, Cambridge, 1956. 276 pp. $4.75.

Theory of Approximation. N. I. Achieser. Translated by Charles J. Hyman. Ungar, New York, 1956. 307 pp. $8.50.

An Encyclopaedia of the Iron and Steel Industry. Compiled by A. K. Osborne. Philosophical Library, New York, 1956. 558 pp. $25.

Momentum Transfer in Fluids. Wm. H. Corcoran, J. B. Opfell, B. H. Sage. Academic Press, New York, 1956. 394 pp. $9.

Elements of Pure and Applied Mathematics. Harry Lass. McGraw-Hill, New York, 1956. 491 pp. $7.50.

Die Technischen Anwendungen der Radioaktivitat. Engelbert Broda and Thomas Schonfeld. Verlag Technik, Berlin, 1956. 313 pp.

Miscellaneous Publications

(Inquiries concerning these publications should be addressed, not to Science, *but to the publisher or agency sponsoring the publication.)*

The St. Anthony Falls Multi-Purpose Test Channel. Tech. Paper No. 17, Ser. B. Lorenz G. Straub and C. E. Bowers. University of Minnesota, Minneapolis, 1956. 19 pp.

The Arzberger Site, Hughes County, South Dakota. Occasional Contributions, No. 16. Albert C. Spaulding. Museum of Anthropology, University of Michigan, Ann Arbor, 1956. 173 pp. $3.50.

Traffic Assignment by Mechanical Methods. Highway Research Board Bull. 130. National Academy of Sciences–National Research Council, Washington, 1956. 77 pp. $1.50.

A Revision of the Genus Nissolia. Contributions from the U.S. National Herbarium, vol. 32, pt. 2. Velva E. Rudd. Smithsonian Institution, Washington, 1956. 34 pp.

Klamath Prehistory. The prehistory of the culture of the Klamath Lake Area, Oregon. Trans. of the American Philosophical Society, New Series, vol. 46, pt. 4. L. S. Cressman. American Philosophical Society, Philadelphia, 1956. 139 pp. $2.

Widening and Resurfacing with Bituminous Concrete. Highway Research Board Bull. 131. National Academy of Sciences–National Research Council, Washington 25, 1956. 46 pp. $0.90.

A Human Engineering Bibliography. Ivan N. McCollom and Alphonse Chapanis. San Diego State College Foundation, San Diego, Calif., 1956. 128 pp.

Erinaceidae from the Miocene of East Africa. Fossil Mammals of Africa, No. 11. P. M. Butler. British Museum (Natural History), London, 1956. 75 pp. £2.

Culture and the Structural Evolution of the Neural System. James Arthur Lecture on the Evolution of the Human Brain, 1955. Fred A. Mettler. American Museum of Natural History, New York, 1956. 57 pp.

Expanding Resources for College Teaching. A report of the Conference on College Teaching sponsored by the American Council on Education, 19–20 Jan. 1956. Charles G. Dobbins, Ed. American Council on Education, Washington, 1956. 137 pp. $1.50.

Meetings and Societies

Council of National Organizations

The Council of National Organizations of the Adult Education Association of the United States met in Atlantic City 7–9 Nov. 1956. The theme of the meeting was an analysis of the personal and social factors influencing individuals to belong to organizations and participate in their programs.

Lawrence K. Frank (formerly director, Caroline Zachary Institute for Human Development) presented the case for the individual factors, whereas Ira De A. Reid (Haverford College) covered the social forces influencing the individual to association. Both men emphasized changing patterns brought on by suburbanization, automation, and mobility of population. They were highly provocative and elicited lively discussion and disagreement on the part of the discussion panel members and the audience.

Melvin A. Glasser (National Foundation for Infantile Paralysis) presented the practical implications of the theme and the preceding theoretical talks to the future work of organizations. Small work groups took up the material from there and made even more specific applications to the programs and membership problems of the organizations the individual delegates represented. Their reports were synthesized and ably presented at the final session by Louis A. Radelet (National Conference of Christians and Jews).

CNO does much more than run an annual meeting. One group has been analyzing and experimenting with techniques for the handling of controversial issues. The TV committee is in the process of developing a year-long series of television and radio programs highlighting social problems and programs with the role of various national organizations emphasized. A grant is being sought for a major study of social trends with particular emphasis on the effects a select number of them may and should have on the programs and activities of organizations. These are only a few facets of a full program developed in the 5 years since CNO was set up as an organ of the Adult Education Association with support from the Fund for Adult Education. The participating organizations have gained a wealth of new ideas through the exchange of experiences in the council.

JOHN A. BEHNKE
Ronald Press Company, New York, N.Y.

New Burakan Observatory

The University of Erevan has had a small telescope for teaching purposes for some years, but, as has happened elsewhere, it has become too small and poorly situated for active astronomical research. Activated by a desire to strengthen Armenian astronomy by obtaining adequate observing facilities, Ambartzumian, who has been recognized as one of the leaders in Soviet astronomy, has, during the past 10 years, directed the erection of a new observatory. This is located about 20 miles north of Erevan at an altitude of about 4500 feet.

The moderate-sized instruments at the Burakan Observatory are of types which are useful in research on stellar statistics, gaseous nebulae, and problems related to stellar evolution—that is, fields in which Ambartzumian is particularly interested. The most impressive are the 21 inch–21 inch Matsutov type Schmidt telescope and the nebular spectrograph with a mirror about 1 foot in diameter. With the latter instrument, Dombrosky discovered the polarization of the Crab Nebula. In addition, the observatory has an 8 inch–12 inch Schmidt, a 16-inch reflector which is used for photoelectric photometry, a 10-inch reflector with a small spectrograph attached as part of the mounting, two small astrographs, and interferometers for radio observations at 4.2 and 1.5 meters. The spectrograph for the 10-inch reflector is equipped with reflection optics and a grating for use in the ultraviolet. Construction has been started on a large parabolic antenna for centimeter-wave radio astronomy. Future plans call for a long-focus visual refractor to complement the small-scale instruments.

This fall, the new observatory was dedicated and its importance was recognized by giving it the status of an institute. This places it directly under the Armenian Academy of Science; it had been merely a part of the Mathematics and Physics Section of the academy. In celebration, a symposium on nonstable stars was held 19–24 Sept. 1956. The high polarization of the light from the Crab Nebula suggests that the emission from this nebula is the radiation of relativistic electrons moving in the magnetic field of the nebula. The emission from other radio sources may have the same origin. Ambartzumian has now proposed that a similar phenomenon may account for the flares and the peculiar ultraviolet continuum in T Tauri and other very young dwarf stars as well as for the emission from some peculiar nebulae.

About 30 participants explored the applications of this hypothesis, detailed the observations which must be satisfied by any theory, and discussed other possible explanations of the observations. The foreign (non-Russian) participants in the symposium were as follows: Jesse L. Greenstein (California Institute of Technology), George Herbig (University of California), and Nancy G. Roman (Naval Research Laboratory) from the United States; Guillermo Haro (Tacubaya and Tonantzintla Observatories) from Mexico; Evry Schatzman (Institut d'Astrophysique, Paris) from France; Vahe Oskanian (Belgrade Astronomical Observatory) from Yugoslavia; and Kung Shu-mu and Shen Liang-tsao (Purple Mountain Observatory, Nanking) from China. The Russians included the three-man Astronomical Council (Michailov, Kurkarkin, and Massevitch) and representatives of the major Soviet observatories as well as others interested in the field. The symposium amply fulfilled its purpose of collecting the knowledge currently available on these problems and outlining profitable directions for future research.

NANCY G. ROMAN
Naval Research Laboratory, Washington, D.C.

Meeting Notes

■ A symposium on the role of solar furnaces in the study of materials at very high temperatures will be held at the Hotel Westward Ho in Phoenix, Ariz., 21–22 Jan. Organized for the benefit of American industry, the program is being sponsored by the Association for Applied Solar Energy, Stanford Research Institute, Arizona State College, Tempe, and the University of Arizona.

Symposium arrangements are being made through John I. Yellott, 3424 N. Central Avenue, Phoenix, Ariz.

■ An international conference on general relativity and the role of gravitation in physics will be held at the University of North Carolina at Chapel Hill, 18–23

Jan. About 40 physicists, 14 of them from foreign countries, will engage in scientific discussions and will pool their information on recent developments in gravitational research.

Most of the conferences will be closed work-shop sessions; however, there will be a "popular symposium" to which the public is invited, at which time phases of gravitational research will be discussed.

■ Peacetime uses of atomic energy will be the topic of the 1957 Nuclear Congress, which is scheduled for 11–15 Mar. at the Philadelphia Convention Hall under the coordination of the Engineers Joint Council.

Four major elements are included in the congress. (i) The second Nuclear Engineering and Science Congress, coordinated by EJC on behalf of 20 engineering and scientific societies, will feature 130 technical papers during a 4-day program. (ii) The National Industrial Conference Board will hold its fifth conference on Atomic Energy in Industry, featuring 12 round-table discussions. (iii) The International Atomic Exposition, sponsored by the American Institute of Chemical Engineers in cooperation with four other engineering societies, will display industry's latest items in the atomic field. (iv) The Fifth Hot Laboratories and Equipment Conference, sponsored by the Hot Laboratories Committee of Oak Ridge National Laboratory, will take place 14–15 Mar. and deal with the operation and development of equipment for laboratories for atomic energy.

Walter G. Whitman of Massachusetts Institute of Technology, president of the American Institute of Chemical Engineers, is general chairman for the 1957 congress.

■ The 11th annual symposium on Fundamental Cancer Research will be held at the University of Texas M. D. Anderson Hospital and Tumor Institute in the Texas Medical Center in Houston, 7–9 Mar. The general topic is "Viruses and tumor growth."

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Society Elections

■ American Society for the Study of Arteriosclerosis: pres., Charles F. Wilkinson, Jr.; v. pres., R. Gordon Gould; sec.-treas., O. J. Pollak, P.O. Box 228, Dover, Del.

■ American Institute of Chemical Engineers: pres., J. Henry Rushton, Purdue University; v. pres., George E. Holbrook, E. I. du Pont de Nemours and Company; treas., George G. Brown, University of Michigan; sec., F. J. Van Antwerpen, 25 W. 45 St., New York 36.

■ Council of National Organizations of the Adult Education Association: chairman, John A. Behnke, American Association for the Advancement of Science; vice chairman, Samuel D. Freeman, National Jewish Welfare Board; sec., Helen M. Feeney, Girl Scouts of U.S.A.

■ Association for Research in Nervous and Mental Disease: pres., Francis J. Braceland; 1st v. pres., Paul Hoch; 2nd v. pres., Carl Pfeiffer; sec.-treas., Rollo J. Masselink, 710 West 168th St., New York 32; asst. sec., Lawrence C. Kolb.

■ American Council of Independent Laboratories, Inc.: pres., Alvin C. Purdy, Bull and Roberts, Inc., New York; v. pres., Cecil M. Shilstone, Shilstone Testing Laboratory, New Orleans; sec., Roger W. Truesdail, Truesdail Laboratories, Inc., Los Angeles; treas., F. H. Wright, Lucius Pitkin, Inc., New York.

■ Radiological Society of North America, Inc.: pres., C. Edgar Virden; pres.-elect, Sydney J. Hawley; sec.-treas., Donald S. Childs, 713 E. Genesee St., Syracuse, N.Y. The vice presidents are Richard H. Chamberlain, Maurice D. Frazer, and Harold P. Tompkins.

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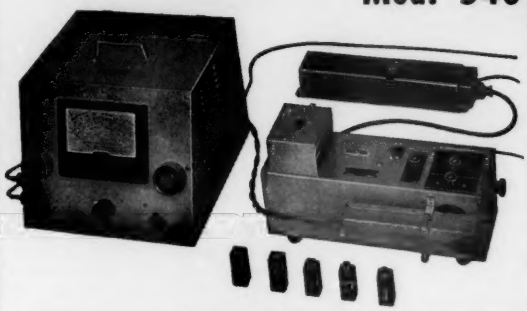

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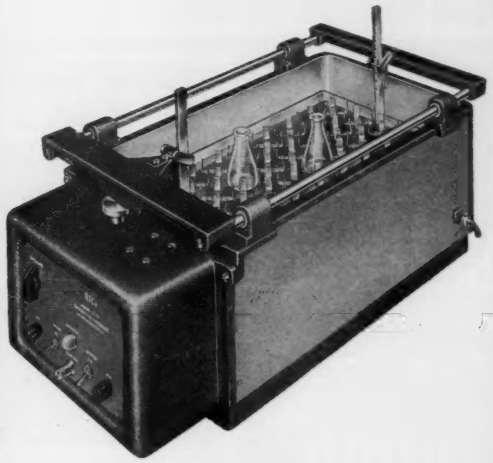

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Forthcoming Events

February

3. American Assoc. of Bioanalysts, 3rd annual Margaret Beattie Lecture, San Francisco, Calif. (W. N. Reich, Walnut Creek-Lafayette, Laboratories, 1625 Locust St., Walnut Creek, Calif.)

4–8. American Soc. for Testing Materials, Philadelphia, Pa. (R. J. Painter, ASTM, 1916 Race St., Philadelphia 3, Pa.)

9–12. Medical Education and Licensure, 53rd annual cong., Chicago, Ill. (E. L. Turner, American Medical Assoc., 535 N. Dearborn St., Chicago 10.)

10–12. Canadian Ceramic Soc., 55th annual, Niagara Falls, Ont., Canada. (L. C. Keith, 49 Turner Road, Toronto, Ont.)

14. Present Status of Heart Sound Production and Recording, symp., Buffalo, N.Y. (R. M. Kohn, Univ. of Buffalo, 2183 Main Street, Buffalo 14, N.Y.)

14. Significance of Nucleic Acid Derivatives in Nutrition, Assoc. of Vitamin Chemists, Chicago, Ill. (M. Freed, Dawe's Laboratories, Inc., 4800 S. Richmond St., Chicago 32.)

14–15. Transistor Circuits, conf., Philadelphia, Pa., (G. H. Royer, Westinghouse Electric Corp., 356 Collins Ave., Pittsburgh 6, Pa.)

15–16. National Soc. of Professional Engineers, Charleston, S.C. (P. H. Robbins, 2029 K St., NW, Washington 6.)

15–17. National Assoc. for Research in Science Teaching, annual, Atlantic City, N.J. (C. M. Pruitt, Univ. of Tampa, Tampa, Fla.)

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18–20. American Educational Research Assoc., annual, Atlantic City, N.J. (F. W. Hubbard, AERA, 1201 16 St., NW, Washington 6.)

18–22. American Soc. of Civil Engineers, Jackson, Miss. (W. H. Wisely, ASCE, 33 W. 39 St., New York 18.)

18–22. Endocrinology: Hormones in Blood, Ciba Found. Colloq. (by invitation), London, England. (G. E. W. Wolstenholme, 41 Portland Place, London, W.1.)

21–23. National Soc. of College Teachers of Education, annual, Chicago, Ill. (C. A. Eggertsen, School of Education, Univ. of Michigan, Ann Arbor.)

23. American Mathematical Soc., New Haven, Conn. (J. H. Curtiss, AMS, 190 Hope St., Providence 6, R.I.)

23. Oregon Acad. of Science, annual, Monmouth. (F. A. Gilfillan, Oregon State College, Corvallis.)

24–28. American Inst. of Mining, Metallurgical and Petroleum Engineers, annual, New Orleans, La. (E. O. Kirkendall, AIME, 29 W. 39 St., New York 18.)

24–28. International College of Surgeons, 10th biennial cong., Mexico, D.F., Mexico. (M. Thorek, ICS, 850 W. Irving Park Rd., Chicago 13, Ill.)

25–28. American Soc. of Heating and Air-Conditioning Engineers, Chicago, Ill. (A. V. Hutchinson, ASHAE, 62 Worth St., New York 13.)

26–28. Western Joint Computer Conf., Los Angeles, Calif. (M. J. Mendelson, Norden-Ketay Corp., 13210 Crenshaw Blvd., Gardena, Calif.)

March

1–2. American Physical Soc., Norman, Okla. (K. K. Darrow, Columbia Univ., New York 27.)

1–3. National Wildlife Federation, annual, Washington, D.C. (C. H. Callison, 232 Carroll St., NW, Washington 12.)

3–6. American Inst. of Chemical Engineers, White Sulphur Springs, W.Va. (F. J. Van Antwerpen, AIChE, 25 W. 45 St., New York 36.)

3–9. American Soc. of Photogrammetry, 23rd annual, joint with American Cong. on Surveying and Mapping, 17th annual, Washington, D.C. (C. E. Palmer, ASP, 1515 Massachusetts Ave., NW, Washington 5.)

4. Wildlife Soc., annual, Washington, D.C. (D. L. Leedy, Fish and Wildlife Service, Dept. of the Interior, Washington 25.)

4–6. National Biophysics Conf., Columbus, Ohio. (H. P. Schwan, School of Medicine, Univ. of Pennsylvania, Philadelphia 4.)

4–8. Analytical Chemistry and Applied Spectroscopy, Pittsburgh, Pa. (L. M. Melnick, U.S. Steel Corp., Applied Research Lab., Monroeville, Pa.)

7–9. Fundamental Cancer Research, 11th annual symp., Houston, Tex. (L. Dmochowski, M. D. Anderson Hospital, Texas Medical Center, Houston 25.)

7–9. Optical Soc. of America, semiannual, New York, N.Y. (S. S. Ballard, Scripps Inst. of Oceanography, San Diego 52, Calif.)

(See issue of 21 December for comprehensive list)

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■ PETRI DISHES containing ready-to-streak culture media are packed in sterile polyethylene bags. Nine different culture media used in routine bacteriology and mycology are currently available. The dishes are disposable. (Hyland Laboratories, Dept. S122)

■ CATALOG OF SILICONES describes approximately 150 silicone products, grouped according to usage. (Dow Corning Corp., Dept. S123)

■ IMPULSE MAGNETIZER generates a field intensity of up to 500,000 gauss. The unit, which has a maximum line demand of 6.6 kva, produces peak impulses of 1500 kva up to 50 msec in duration. (Raytheon Manufacturing Co., Dept. S130)

■ ELECTRON MICROSCOPES are described in a new brochure. The electron optical system, pumping unit, electronic circuits, condenser, aperture, beam wobbler, objective lens, and astigmator, as well as other components, are described in the illustrated booklet. Operating controls and various cameras that can be used with the instruments are also covered. (North American Philips Co., Inc., Dept. S133)

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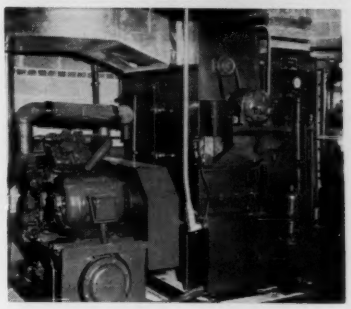

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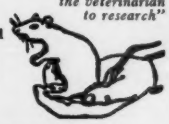

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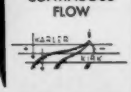

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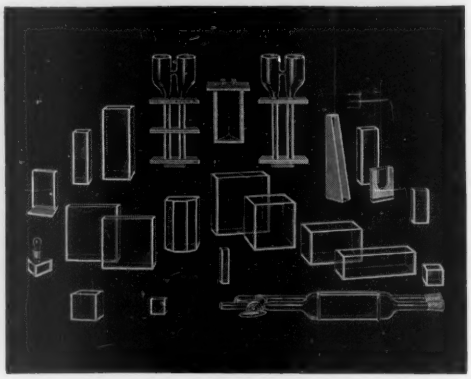

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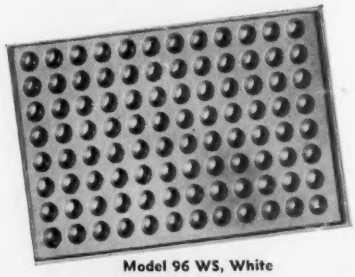

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Edited by: **Eleanor E. Buckley,** Medical Department, Wyeth Laboratories; and **Nandor Porges,** Eastern Regional Research Laboratory of the U.S. Department of Agriculture, Philadelphia, Pennsylvania.

6 x 9 inches, 480 pages, 113 illustrations, index, clothbound, 1956. Price $9.50. AAAS Members' prepaid order price $8.25.

A symposium volume of the American Association for the Advancement of Science.

The more than sixty scientific papers included in this volume were presented at the first International Conference on Venoms during the AAAS Meeting in Berkeley, California. The authorship spans the globe, and the coverage of all aspects of the problem is equally comprehensive.

E. R. Trethewie of Australia reports experimental studies on certain pharmacological antagonists used in an effort to prolong life, providing more time for therapeutic measures. B. W. Halstead of the College of Medical Evangelists in California covers present knowledge on poisonous fishes. H. A. Reid of Malaya describes clinical effects of the bite of the sea snake (Enhydrina schistosa) in three fatal cases. Giovanni Favilli of the University of Bologna, Italy, discusses spreading factors in animal parasites and venoms, and some properties of hyaluronidase. The last subject is also covered by Paul Boquet, of the Institut Pasteur, in Paris. B. R. Criley and associates, of the Wyeth Laboratories, Marietta, Pennsylvania, describe the development and standardization of a multivalent refined antivenom for the family Crotalidae. The final article by H. L. Keegan of the U.S. Army Medical Corps presents an invaluable list of all known antivenins available throughout the world for all types of poisonous bites, with information on producers, sources, indications, dosages, and other details. The random selection is only a small sample of the wealth of valuable material by outstanding world authorities.

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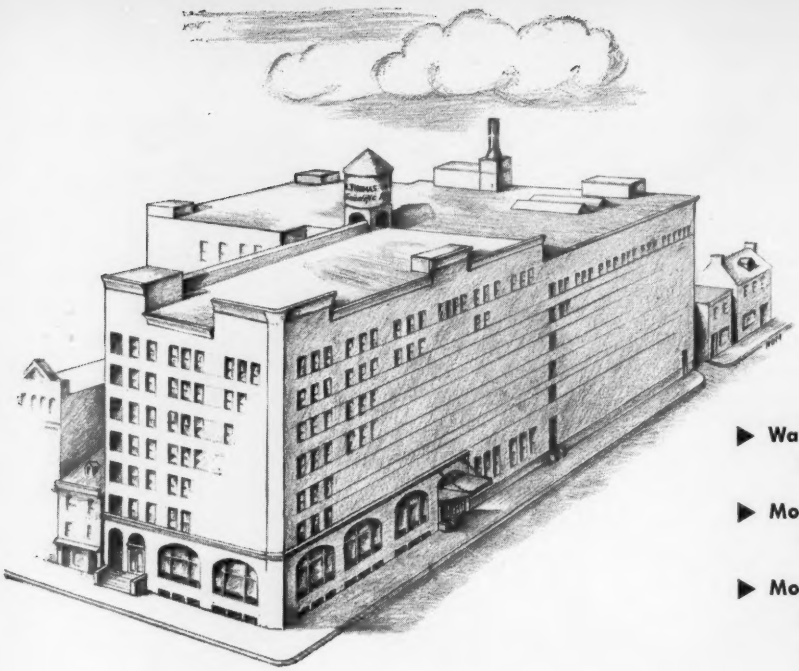

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